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THE INTERNAL SECRETIONS  
IN PRACTICAL MEDICINE

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# THE INTERNAL SECRECTIONS IN PRACTICAL MEDICINE

BY

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Dedicated to  
**Charles E. DeM. Saenger**  
**M. D., LL. D., Sc. D.**  
**of Philadelphia**

to whom, more than to any other man, practicing physicians in the United States are indebted for painstaking and persistent efforts to make clear the importance of the glands of internal secretion through his book, "The Internal Secretions and the Principles of Medicine," and his numerous other writings; and for directing attention to facts concerning the functions of these organs which, though long discounted by some, are now increasingly being accepted by the profession.

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## PREFACE

A NUMBER of physicians, especially those who have read or heard one or more of my papers on subjects related to the glands of internal secretion, have expressed a desire to have some of them available in more permanent form. Hence this collection of articles in book form.

Unlike my earlier book, "Practical Hormone Therapy: a Manual of Organotherapy for Practitioners" (which is referred to occasionally in the following pages), the units comprising this collection were not written originally with the intention of fitting them together as harmonious and consecutive whole. As a result of this there is a certain amount of redundancy which it has seemed best to leave unmodified. As these reiterations have been reread for publication in this present form, the fact has been emphasized that no harm can come from reading some essential more than once, especially when the repetition lends weight to some particular contention in one paper and to a different one in another.

Several additional paragraphs have been added to a number of the articles as originally published in the medical press, with the idea of making them more comprehensive and as up-to-date as possible. As a matter of fact quite a number of experiences have been reported in current literature which amplify my position in a previously published report,

and their inclusion here adds emphasis to what may have been said.

No attempt has been made to cover the entire subject. It is far too vast. In fact it would take a small library to include all the information now at our disposal regarding the glands of internal secretion and their hormones. However some time has been spent in preparing a fairly complete index so as to facilitate the study of various phases of the subjects covered which may be of immediate interest to the reader and yet be discussed in more than one chapter in the book.

For a more complete consideration of the therapeutic side of this subject the reader is referred to my book mentioned above; and also to a quarterly journal entitled "ENDOCRINOLOGY" which is a periodical review of the current literature on all phases of this subject. This journal is published by the Association for the Study of the Internal Secretions, which I assisted in starting in 1916. Further information regarding the activities of this Association will be sent to any interested physician on request.

My thanks are due to a number of colleagues for the encouragement given me to have these papers collected in this form, as well as to the publishers of various medical journals in the United States and Great Britain in which some of the chapters already have appeared, for the privilege of reprinting them in this form.

I realize that some of my statements are open to criticism, and I will welcome any constructive critical remarks or queries. I do not profess to be more than an ardent student of what is to me a very fascinating subject.

I need not apologize for my interest in this subject, nor for the enthusiasm it has engendered. I only hope that some hint in this book may serve to make a real difference to some reader's consideration of a difficult case; and that as a result of reading it some tangible advantage may accrue to both patient and physician.

HENRY R. HARROWER.

Glendale, California.

July, 1917.



# THE INTERNAL SECRETIONS IN PRACTICAL MEDICINE

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## I

### INTRODUCTION: BROADENING THE SCOPE OF THE PRACTICE OF MEDICINE

AS our knowledge of physiology becomes more intimate and our application of some of the ideas set forth by the experimentalists are put into practice, we find the scope of medical practice broadening in a remarkable manner. Revolution follows revolution until the standardized procedures of to-day differ as radically from those of, say, 25 years ago as do the present conceptions of the physiologic relations of the various parts of the body compared with those held at that time.

Undoubtedly the most radical as well as important advance in medicine is our better knowledge of the endocrine system—that interlocking, though widely separated, collection of glands of internal secretion which we now know is in supreme control of growth, both physical and mental; metabolism; the sympathetic nervous system, with its regulation of vascular tone and blood pressure; as well

as the indefinite and complex factors gathered together into the one well-known term "constitution." The hormones produced by these wonderful glands are secreted into the blood and serve to correlate function and harmonize many of the widely differing functions of the body. Their chemical messages are of such a nature that to ignore them and their subtle influence is to miss a very large and important part of the information which may be at the disposal of any observant physician.

Just as the discovery of the hormones and the unravelling of the intricate skein of their relationships has revolutionized physiology, so the knowledge we have been able to deduce from these facts is revolutionizing therapeutics, for it is now generally recognized that organotherapy is making possible the successful treatment of many chronic and complicated disorders.

The study of these endocrine glands will well repay the interested reader of the hundred and one articles and abstracts now appearing in current medical literature; and as he applies the obvious treatment in a given case, he will be both surprised and pleased at the results which so often follow the application of this altogether scientific and reasonable branch of therapy.

It is not necessary within the limits of this brief introduction to do more than direct attention to

the great possibilities of this phase of medicine; and to outline the essential facts upon which the science of practical hormone therapy has been built.

By far the greatest principle is that of "homostimulation," which is included in what has come to be known as Hallion's law, which is as follows: "Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient it is conceivable that this influence augments its action and, when it is injured, that it favors its restoration." This has been demonstrated experimentally and clinically so many times, that it is almost axiomatic, though it is not infallible, and may still be criticized occasionally by some. Granting what Hallion has said, functional insufficiencies of many of these organs may be expected to be favorably influenced by giving suitable doses of the corresponding gland secured from animals.

Closely allied to this is another slightly different phase of organotherapy. Frequently it is not sufficient to attempt to stimulate a lagging gland. One must replace, in part at least, the missing substance that it should have been furnishing to the body. This is what is known as "substitutive organotherapy." In conditions like cretinism or infantilism where the thyroid or gonads are absent, one can measurably restore the activity that is reduced or absent because of the lack of the hormone stimuli

from the glands in question. In severe functional conditions we expect to benefit from organotherapy in at least two ways—by substituting for the missing hormones and, also, by causing what is known as homostimulation, the principle so well described in Hallion's law just quoted.

Again the chemical substances produced in the normal physiologic action of certain of the ductless glands have a definite pharmacological action and its application in medicine is the so-called "specific organotherapy," for the influence of the drug—these extracts must be considered purely as drugs—favors some desirable action as, for instance, the stimulation of the uterus with the posterior pituitary principle during a delayed labor. In such a case there is no evidence whatever to prove that this hormone principle is absent or even that the pituitary is not working normally. We simply make use of the specific action of this substance.

Finally in our clinical and laboratory experimental work we have found that the administration of certain "extracts" (as they are usually but, in some instances, erroneously, called) cause certain physiologic reactions and we make use of these facts by applying what is, strictly speaking, "empirical organotherapy."

No matter in what conditions organotherapy may be used, irrespective of its "scientific" or its "empirical" basis, it is a valuable addition to our

medical armamentarium, for where its application is physiologically proper one may expect it to give results and therefore be rational, while in the not infrequent cases where there may be a question about the the exact *raison d'etre* of a certain organotherapy remedy, it is rational because it is resultful. "We care not how the results come, provided they come, and come quickly."

Organotherapy, however, is only a small part of endocrinology; a part of it which has not yet recovered from the rank empiricism and quackery of a few decades ago. The study of the relations of the glands of internal secretion whether followed by the application of organotherapy procedures or not, is of great importance; and as various phases are considered from certain practical points of view, it will be clear that the remark of one writer—"in these days the internal secretions are being studied as never before, and most assuredly are coming into their own"—is perfectly true; and that there is plenty of excuse for the widespread interest now being accorded to this growing branch of medicine.

The more time and attention that is given to the practical study of endocrinology, the broader will be the scope of the practice of medicine and the greater the professional prestige and profit of the aggressive physician who measures and applies the advances in medicine by the only reasonable standard—the standard of "tests-and-results."

## II

### THE INTERNAL SECRETIONS WITH SPECIAL REFERENCE TO THE TREATMENT OF CHRONIC DISEASE

THE rapidly increasing fund of information which students of endocrinology are making available for interested members of the profession, is modifying many of our conceptions of internal medicine as well as changing some of our ideas regarding treatment.

As we bring these facts to bear upon numerous and widely differing phases of medical practice, it soon becomes clear that a great fundamental principle is involved, which neither the skepticism of the ignorant nor the passage of time can change. The hormones, or active principles elaborated by the glands of internal secretion, exert a decided influence upon those factors concerned in the causation as well as the cure of the majority of chronic diseases. Hence, hormone therapy, or the use of animal extracts in therapeutics, contains potentialities worthy of practical consideration by those who treat the numerous persistent and intractable ills which the flesh seems to be inheriting in increasing degree.

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An address read before the Southern California Medical Society at Los Angeles, California, December 2nd, 1915.

The subject is still in its formative stage, and occasionally one finds those who look at it askance, despite the innumerable encouragements which we are constantly meeting from day to day. I just happened to pick up the current issue of the American Journal of Obstetrics (Nov., 1915, p. 885), and read an interesting discussion on the value of corpus luteum therapy. One of the participants, Dr. A. T. Jones, of Providence, made a statement which I would like to repeat: "With reference to organotherapy, I think the profession is divided into two classes. As a rule one class loses its head over organotherapy and believes everything can be cured by organic extracts"—and, by the way, I have been put into this class because my recent book, "Practical Hormone Therapy," merely for the sake of comprehensiveness, takes up some forms of organotherapy with which I have no experience, because I have little faith in them—"while the other class is that group who would not give organic extracts even if they knew they were going to get a good result. They will not take it up; they never have tried it. I believe these extracts are of value, and particularly the corpus luteum extract."

The writer fully agrees with Dr. Jones, and while one meets more men who should be in the second as compared with the first class, I am finding an increasing number of progressive physicians who are open to conviction and who, realizing the vast possibilities of this study, are exploring its depths and

finding many most pleasing experiences there. In the same discussion just referred to, Leighton, in concluding, said: "This therapy has its limitations. It is not a cure-all. There is one trouble, and that is we do not use it enough!" And this applies in other equally practical phases of the subject to which brief allusion shortly will be made.

With very few exceptions, all chronic diseases have associated with them, and are aggravated by, a disturbance in one or more of the internal secretory organs. If this position is correct, we have another angle from which to consider those of our patients who are chronic sufferers. Many articles and editorials in our own and foreign medical literature (and, parenthetically, it must be admitted that abroad they do more work in this line, hence more information is to be found in the French, Italian and English literature) direct attention to the new avenues of therapeutic endeavor that are being opened up. And they are being well traveled. Organotherapy is being studied as never before, and those who are attracted by its fascinations, are learning that the results sometimes attained are not simply good, but wonderful.

You all have personal knowledge of the diverse therapeutic possibilities of the principle from the infundibulum of the pituitary body first suggested as a remedy by Blair Bell, of Liverpool, as late as 1909. You know of its startling effects upon the uterus in labor and of its value as a postpartum

remedy, its influence in such remote conditions as intestinal paresis, anuria and agalactia; and finally of its definite value as a heart tonic. In fact in a personal letter from the late Sir Lauder Brunton, he remarked that pituitrin was a more efficient heart stimulant than either digitalis or strychnia, and it is none too often used for this purpose either. Now I have not enumerated all the advantages of this single remedy and there are other organo-therapeutic preparations almost as wonderful.

None the less to some "it is still too early to pass judgment," and as another put it, "we are still groping in the very dimly lighted recesses of this new study." However, it is encouraging to recall that a single experience is worth ten times as much as an argument; and the tests-and-results method is the only way to convince one's self that what may be said here to-night is not just the dream of a visionary crank.

Obviously we cannot more than refer to the mere fundamentals involved in the relation of the internal secretions to the incidence and control of chronic disease. We can, however, refresh our minds on a few of the better known matters and, perhaps, hint briefly of some of the other possibilities of this rapidly advancing and increasingly interesting subject.

Probably more has been written about the thyroid than about any of the other glands of internal secretion. It has been most carefully studied for

many years and its pathology and physiology are only just beginning to be fairly well understood; in fact, though this is probably the best known of the endocrine glands, we are not yet able to isolate its active principles,\* and we have still much to learn of the intricacies of its physiologic relations. The epoch-making work of George Murray, now of Manchester, in the original application of thyroid therapy in the major thyroid disorders myxedema and cretinism, seems to have directed attention far beyond the much more common minor thyroid insufficiencies, and evidence of this is found in the last U. S. P., for in it the dosage of desiccated thyroids is given as 5 grains, an altogether preposterous dose in the majority of the conditions in which thyroid is now used. Instead of this pharmacopœial dose, which, by the way, may be quite reasonable in certain cases of athyroidia and severe thyroid disorders, we now rarely use more than one grain and frequently a quarter or half a grain three times a day is quite sufficient to bring about very satisfactory results.

The thyroid gland is functionally disturbed, slightly in some cases, more in others, in many every-day conditions, many of which are chronic in their manifestations. Those disorders which are dependent upon perversions of the metabolism—

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\*Since this was written a communication from the Mayo Clinic by E. C. Kendall announces the discovery there of what appears to be the active principle of the thyroid gland.

rheumatism, gout and perhaps, in some degree, diabetes—usually have a thyroid element of greater or less importance. Following the original work of my very good friend, Dr. Eugene Hertoghe, of Antwerp, Leopold Levi and his associate, Baron Henri de Rothschild, of Paris, have made a most minute study of the part that the thyroid plays in almost every disorder. Every patient who comes to their hospital virtually is studied as a thyroid case, and in their recent book, "La Petite Insuffisance Thyroidienne et son Traitement," it is remarkable to note how large a variety of conditions have a distinct thyroid aspect and, more practical yet, are either directly benefited by the administration of thyroid or the regular treatment is made more effective by the addition of one or two centigrammes of thyroid per day. More than forty disorders are in this category from neurasthenia to psoriasis. Yet, like most enthusiasts, they have been laughed at, and sneered at, too, for fifteen years or more. Still Levi and de Rothschild have mastered the technique of thyroid medication and use it with much advantage in many conditions, both distinctly thyroid in origin and in which no obvious thyroid disturbance can be found. In this country we have still a few things to learn in this particular corner of this field.

Closely related to thyroid hypofunction is the condition known as pluriglandular insufficiency, an extremely common symptom complex which is

more than occasionally overlooked. The statement recently has been made that disorders of the hormone-bearing organs always affect more than one gland, since the intimacy of these organs renders it impossible for one gland to be disturbed without an associated disturbance in one or more of the others related to it. There are two principal forms of pluriglandular insufficiency, the organic and the functional. The former commonly asserts itself in certain developmental disorders and in syphilis. Right here is a phase of syphilology which deserves closer attention. In a paper which I prepared for a special issue of *The Practitioner* (London), on Pluriglandular Insufficiency,\* a number of reports were collated showing the relation of syphilis to ductless glandular syndromes. In such cases the information has usually been elicited at the autopsy table, though several cases of obvious endocrine disorder were traced to syphilis and treated with comparative satisfaction. The chief deduction that may be made from this is that syphilis as a generalized disease, may and does affect the hormone producing system and its treatment may be extended by adding to the usual arsenic or mercury treatment, suitable organo-therapeutic extracts to stimulate the various semi-active ductless glands and thus cause a general betterment not otherwise attained.

In this connection an abstract in the *Journal of*

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\*Chapter V of this book.

the American Medical Association (October 2, 1915, p. 1223), is instructive. "A striking case is reported by Korczynski in which inherited syphilis seems to have impaired the functioning of the thyroid, hypophysis, ovaries and blood-producing organs. The child was mentally backward. Thyroid treatment and treatment for syphilis were given together, and a pronounced change for the better was soon apparent and has continued to progress. . . ."

The functional forms of pluriglandular insufficiency are not associated with the obvious manifestations that the more marked organic conditions usually show. The reduced production of the "chemical messengers" is none the less present, for when an individual is run-down, for instance, when the elimination is not as it should be, when the muscles are easily fatigued, the nerves easily excited and there are present the other usual manifestations of neurasthenia and debility, one can hardly believe that the glands of internal secretion alone are working normally. In such cases pluriglandular therapy is an exceptionally useful treatment, alone or combined with other treatment which the exigencies of the case may indicate. It may be well, incidentally, to remark that in ovarian disorders where luteal therapy is indicated and likely to be effective, the addition of some of the extracts of glands known to be intimately related to the gonads, the thyroid and the pituitary, will more

than likely make the response to treatment more decided and resultful.

The control of the sympathetic nervous system by the chromaffin hormone produced in the medullary portion of the adrenal glands, makes these organs of supreme importance in numerous conditions. Take that most common of all clinical manifestations, pain, and recall that it has been shown by competent investigators to be a decided stimulant to the adrenals and thus "wears them out." This is a partial explanation, at least, of the clinical value of preparations of this character in many disorders including cholera (with its extreme pain and collapse), shock (with its associated acute adrenal insufficiency first intelligently discussed by Sajous, of Philadelphia about 13 years ago), post-febrile collapse or asthenia (conditions definitely traced to hypoadrenia and just as definitely benefited by the obvious therapeutic procedure—the administration of adrenalin or similar products), and other important disorders.

Crile's valuable studies which have given us anoci-association and the power to reduce or entirely eliminate post-anesthetic shock by removing the stimuli which unduly overwork the kinetic system, are based in a large measure upon the physiological chemistry of the adrenal medulla, and while his most profitable work has been of a prophylactic nature—to prevent the unpleasant results at one time not infrequently following operations, the

same principle applies in therapeutics, for when the adrenals have been depleted and the body is suffering from the lack of the normal amount of adrenin, with low blood pressure, asthenia and collapse, the natural thing to do is to secure the missing substance from animals and give it as quickly and directly as possible, just as we have learned to do the same thing with thyroids from sheep or corpora lutea from sows.

Now you realize, of course, that this subject which was chosen on the spur of the moment as the result of a telegraphic request by your Secretary to my friend, Col. McCullough, of the Surgeon-General's Library in Washington, has been considered only in its broadest general aspects. It is as broad as the influence of the hormones upon physiology, and the limits of its practical usefulness have not yet been reached, although we have already learned many, many things.

There is much more, and the more we study and apply these principles in our work, and especially that part of it which concerns the treatment of chronic disorders, the more we appreciate the enthusiasm of many who are daily delving into these secrets and are finding in them so much that is available in the every-day routine of medicine.

### III

## THE RELATION OF THE ENDOCRINE GLANDS TO FUNCTIONAL DISORDERS

WHILE the study of the glands of internal secretion has received a great impetus in the past few years, and the science underlying the diagnosis and treatment of endocrine disorders certainly has advanced greatly in this period, there is still a well-defined tendency to consider ductless glandular disease *per se* rather than the functional pathology resulting from modifications in the chemical activities of these glands.

Disorders of function obviously are of far greater clinical importance than organic disease not merely because of their much greater frequency, but because the former are merely more or less slight aberrations from the average, whereas the latter involve structural changes which in many cases are only partially amenable to the very best of treatment.

The discovery of cretinism, myxedema, the Addison, Froehlich or Graves syndromes is comparatively easy, for each of these conditions is a disease with a more or less definite pathology and symptomatology. But the insidiousness of func-

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Read in a Symposium on Functional Pathology before the Sections on Medicine and Neurology, California State Medical Society at Coronado, April, 1917.

tional pathology of the glands of internal secretion and the frequency with which disturbances of their functions play a part in many acute as well as chronic conditions of every day occurrence, makes their study of greater clinical importance than the more definite and easier demonstrated ductless glandular diseases of which a few have just been enumerated.

With our added knowledge of the physiology of the endocrine glands and its importance, we are enabled to study many a functional condition from a viewpoint which is considerably different from that of past years, and this may enable us so to modify our treatment that many of the hitherto intractable disorders may now respond to our efforts.

In an editorial in the New York Medical Journal (1) published a few months ago, the importance of functional medicine was emphasized and it was remarked that in order that the advances in the pathological sciences might be fully appreciated and be of the greatest usefulness "there is need for a better understanding of fundamental physiological principles and a much wider appreciation of functional possibilities. To this must be added the ability to correlate new findings and to detect departures from the normal in their early stages. It is only from such studies as these that we may hope to acquire that breadth and keenness of vision so essential to-day to offset the narrowness and con-

centration of specialism." As a result of this, in the words of the same editorial writer just referred to, "our diagnoses will become more fundamental and our therapeutics more vital."

I have seen many a case with the diagnosis of rheumatism or tuberculosis or neurasthenia or indigestion in which the ductless glandular element was not even thought of. Why should a physician study the thyroid activity of a patient with tuberculosis, or connect the adrenals with neurosis? As a matter of fact, it is impossible for a severe infection like rheumatism or a protracted disease like tuberculosis not to make a very decided mark upon one or more of the glands of internal secretion, and since these glands respond so easily to the influence of infections, toxemias or even psychological states, it takes but a short time to involve them.

It can be taken for granted that questions concerning therapeutics always must be matters of opinion in which unanimity is unlikely; but questions of pathologic physiology are now being ascertained with precision and the subject is being put upon such a basis that dissent is not so probable. At least the relations of certain functions of the body are now sufficiently understood so that we can refer to them with confidence and it is to some of these that I wish to direct your attention to-day.

Every function of the body is in some way directly or remotely connected with the work of the endocrine glands, hence disorder in them invari-

ably, let me emphasize this word, spells disorder in other functions. So really the functional pathology of the endocrine glands is reflected in almost every phase of the practice of medicine, for growth, metabolism, oxidation, resistance to infection and the more indefinable but none the less important fundamentals, constitution and temperament, are now considered to be dependent upon ductless glandular action.

Furthermore the clinical leading of information of this character prompts us to use measures in the place of or in conjunction with those to which we have become accustomed, and such modifications of the treatment are a decided advantage towards greater success. In other words, when we are considering a given disease we will find out more of value and be able to render a more satisfactory service if the functional pathology of the endocrine organs is also considered—if we consider the patient as a whole rather than his disease as a unit. As yet, however, this is not the rule, for there still seems to be a tendency to study diseases instead of patients, and to treat certain text-book symptoms with whatever measures may be uppermost in the physician's mind.

Our knowledge of clinical endocrinology might be considerably better, at least in so far as discerning the earliest beginnings of these subtle influences is concerned. It is not in the discovery of well-differentiated disorder, but in the appreciation

of the ordinary chemical changes of the beginnings of disease—the early steps in functional pathological change—that one attains the best results and the greatest personal satisfaction.

In an editorial note on cancer, Clinical Medicine (2) remarks: "We still are in constant protest against the neglect of the study of physiology now prevalent in the entire profession. Over and over again we have urged upon the profession the importance of so studying the physiology of the human body that the very first departure from normal activity of any of the functions shall be detected and the cause of such departure removed. . . . To the chemistry of the blood, we must look for the essential cause of cancer."

Physiology is too complex for internal medicine, much less the other branches of medicine, to be reduced to one single phase of study. The broader our conceptions of the physiologic functions of the body, the more intimate is our knowledge of the cellular interrelationships of the various integral parts of the organism; and hence the greater is our appreciation of the importance of more or less insignificant modifications of these relationships—or "functional pathology" as it is called.

Since we have begun comparatively recently to realize the comprehensiveness of the so-called "hormone balance," we have also naturally had our eyes opened to the importance of aberrations in one or more of the elements which go to maintain

this balance; and disordered function, be it ever so slight, now frequently directs attention to an insignificant thyroid, pituitary or other endocrine complex which until very recently invariably was overlooked.

It may not be possible to substantiate this position in the mind of every skeptic in the brief time allotted; but we might take up, say, half a dozen constitutional diseases such as we have to meet every day, and reiterate some opinions which seem to establish that the endocrine element in these is prominent (in varying degree depending upon the physiological substratum of the individual and their reactivity to the fundamental causes of disease) and, therefore, of no mean clinical importance.

I propose to refer to rheumatism, epilepsy, neurasthenia, diabetes, tuberculosis and syphilis; and though each is a subject worthy of a comprehensive discussion, I will gather together some hints which I hope may remain with you after this meeting is over:

**Rheumatism** is “a constitutional disease with local manifestations.” Some say that it is due to an infection, others to uric acid, still others to acidosis. Each may be correct, for there are almost as many forms of rheumatism as there are rheumatic patients. If it is an infection with the s. *rheumaticus* or other microorganism, the thyroid, as an important part of “the powers of resistance” of the

body, is concerned. If it is a toxemia the adrenals must be influenced in some way, for of all the organs in the body, endocrine or otherwise, the adrenals are the most susceptible to toxins—they react on the slightest provocation, and are largely responsible for the well-known sympathetic manifestations of toxemia.

The thyroid is more often implicated than any other endocrine organ, and subthyroidism many times is the one and only cause of what is supposed to be rheumatism. The sluggish metabolism of the rheumatic is so nearly like that of the cretin or myxedematous patient (and responds equally to indicated treatment) that I believe the French (Gauthier, Gilbert, Carnot and Leopold Levi) are right in emphasizing thyroid dyscrasia as an actual cause of "rheumatism." (3)

As one acquires the habit of considering rheumatism from this angle, it is surprising how many of the clinical signs of thyroid insufficiency are discovered. And it is equally true that attempts to control these associated manifestations, often simultaneously benefit the more decidedly rheumatic symptoms.

Whenever you meet rheumatism, especially the chronic forms, at least think of the thyroid and its possible relations to it.

Epilepsy is one of the profession's "hardest nuts" and is not "easy to crack." Probably there are factors involved that we know very little about as yet,

such as the presumed bacillus epilepticus, the effects of allergy and the cause and effects of the cerebral edema which seems to be present. Many clinicians have discovered threads connecting epilepsy with the endocrine glands—the thyroid has long since been supposed to play some part in some cases,\* the parathyroids are implicated in many other convulsive conditions, perhaps also in epilepsy. Just a few weeks ago H. A. Knox (4) in a paper on "Research in Epilepsy" reports fairly good results in 30 cases of epilepsy which were treated with desiccated parathyroids (2 grains three times a day, increasing each dose by 2 grains each month) and calcium lactate (1 dram of the saturated solution daily). The adrenals are played upon so invariably by the alimentary toxemia, the most prominent of all the findings in the disease, and so progressive a man as Cotton of the New Jersey State Hospital, of Trenton, is treating scores of cases (69 were recently reported) by keeping this particular relationship in mind. (5)

Perhaps the gland that is receiving the most attention at present is the pituitary, and it seems to be affected more than rarely and, too, pituitary feeding is reported to have proved very useful (6) and several personal experiences confirm this. Suffice it to say that the glands of internal secretion

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\*The subject of the relationship of the thyroid gland to epilepsy is more fully discussed in a recent paper by the author. (See Chapter XII.)

are so often involved in epilepsy that they are our most promising field of present research in unraveling the mysteries of this disease.

Whenever you have to treat epilepsy, don't forget the glands of internal secretion. To do this may alter your treatment in a most salutary manner.

**Neurasthenia** has been called a "cloak with which to cover slipshod diagnoses"—scientifically speaking, there is really no such thing. But the patient won't believe this, for something is certainly wrong when they are supposed to have "neurasthenia" and that "something" is of a chemical rather than a nervous character. Cannon's work on the relations of the emotions to adrenal activity is destined to clear up many of our hazy conceptions of functional pathology. It is a big subject and Cannon has written a whole book on it; (7) but it must suffice to say that neurasthenia really seems to be nothing more nor less than a manifestation of functional dysadrenia. Permit me to read you two quotations\* before we leave this:

"The typical neurotic generally has, if not always, disturbance of the thyroid gland. The typical neurasthenic probably generally has disturbance of the suprarenal glands on the side of insufficiency. The blood pressure in these neurasthenic patients is almost always low for the individuals,

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\*The second quotation 9 (from Kinnier Wilson's writings) will be found on page 89 of Chapter VII.

and their circulation is poor. A vasomotor paralysis, often present allows chillings, flushings, cold or burning hands and feet, drowsiness when the patient is up, wakefulness on lying down and hence insomnia. There may be more or less tingling or numbness of the extremities." (9)

Whenever you encounter a neurosis, try to fix connecting links between it and the endocrine glands; and you may succeed more times than you will fail.

**Diabetes** is an endocrine disease—that is, if we believe that the pancreas has an internal secretory function as the physiologists have most conclusively shown. The so-called Allen treatment not merely reduces toxemia (which excites the adrenals) but saves the pancreas (which is antagonized by the adrenals) and thus "acts both ways." The successful treatment of functional diabetes mellitus—not that form of the disease which is due to serious structural change as in the diabetes of youth, cancer of the pancreas, etc.—embodies three things: (1) relieving the pancreas of as much work as possible, (2) increasing the pancreatic internal secretion if this be feasible, (3) removing toxemia and modifying the nervous circumstances (stress, worry, mental fatigue), thereby reducing adrenal excitability.

**Tuberculosis** is never a local affair; it can not be. Hence the general reaction, whether toxic, febrile, afebrile or nutritional, or all of these combined, also

affects the endocrine glands for they are a part of the body, and, in fact, they are the most sensitive part of the body.

It is strange that as yet only a few men, of whom Dr. Pottenger here is probably the most aggressive, are taking this fact into consideration. We have such a big fight on our hands that all we can see is hygiene, diet and tuberculin. Now all of these are splendid, but why not seek out the changes of chemistry due to the effects of the tuberculosis on the endocrine glands? Are there no evidences of endocrine involvement? For instance in long drawn out chronic disorders asthenia is uniformly present, why not endocrinasthenia? This new word has heretofore been called "pluriglandular insufficiency" and it represents an almost universal concomitant of tuberculosis.

We must not forget to mention the frequency with which the picture of dysadrenia is prominent —hyperadrenia is common, with the circulatory irritability, heart excitement, alimentary spasm and occasional digestive crises. Later hypodrenia is invariably present with asthenia plus, subnormal temperature, low blood pressure and deficient sympathetic tone.

I am not saying that the appreciation of these endocrine features of tuberculosis is going "to revolutionize our conceptions of this disease," but I do say this:

When you see tuberculosis remember "endocrin-

asthenia" and if direct measures are taken to offset this phase of the symptomatology of tuberculosis, surely no harm will have been done.

**Syphilis**—the great toxemia, is probably responsible for more organic or structural diseases than any other single cause. And what is true with bone, nerve, muscle and, in fact, all tissues, is equally true of the endocrine glands. Many a pituitary tumor or brain condition influencing this gland is of luetic origin. Many a "hidden syphilis" is insidiously affecting function and this does not miss the endocrine glands even if it may not be causing actual structural change in them.

I am convinced that at least a part of the constitutional manifestations of syphilis, and especially those which may be connected with the sympathetic nervous system, are directly the result of endocrine changes resulting from the toxic effects of this infection.

We know that syphilis has the peculiar capacity of wreaking its vengeance on the innocent; and fully one half—I am speaking offhand—of inherited endocrine defects, functional or organic, are traceable to syphilis.\* The feeble minded, the defectives, the incompetents and many who may not be so decidedly marked, but none the less have a facility for functional derangements—whose con-

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\*This is probably an overstatement, though lues is certainly a universal scourge; and is often a factor in ductless glandular troubles.

stitutions are "not right"—in reality may be suffering from the inherited defects caused by syphilis.\*

Whenever you discover syphilis, look for its chemical effects—the functional pathology that it so often causes and, too, whenever you find well-defined organic endocrine disease think at once of syphilis and keep on thinking of it until it is ruled out, or no longer a question.

In closing I will take this excellent opportunity to offset a tendency to discount statements which seem to indicate that I "see ductless glands in every case," as one man put it the other day, by reminding you that there are ductless glands in every case! I will supplement this by adding that they are very important and responsible little organs, for not only do they serve the body and suffer with the body; but when their first pathology is discovered and suitably treated, a new aspect many times is put upon a case.

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\*This does not necessarily mean that the unfortunate actually has inherited syphilis, although it is too often discoverable by our present methods of clinical research.

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## IV

### THE INCONSPICUOUS, EVERY-DAY FORMS OF THYROID INSUFFICIENCY

THE so-called "minor thyroid insufficiency" occurs in the routine work of every physician, every day. Very often it is entirely overlooked. It is the principal cause of quite a number of widely varying conditions and a factor of importance in many others. The thyroid gland has been aptly called "the keystone of the endocrine arch"; and we are beginning to realize that the glands of internal secretion play a much more important role than many of us had hitherto imagined. In fact, they are the prime factors in the regulation of metabolism; dominate the nervous system, more especially the sympathetic; and are altogether indispensable to the maintenance of the physiologic harmony of the body.

Our interest in these glands, then, by no means should be limited to the mere consideration of definite disease in one or more of them. We should seek rather to appreciate the insidious and insignificant minor aberrations from the normal, and in so doing in many cases we will be able to forestall the more serious organic manifestations which later assert themselves. (My use of the word "in-

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significant" refers rather to the ease with which these conditions are appreciated, than to their comparative importance, for these aberrations are certainly much more important than yet appears to many physicians.)

As we occupy ourselves in searching for the early, minor manifestations of internal secretory disturbance, we will be able not merely to forestall the more serious organic diseases, but will discover that unsuspected associated symptoms, from chil-blains to nocturnal enuresis, or rheumatism to melancholia, will be modified by organotherapy measures which may have been directed at some entirely different condition.

Most of our practical information on this subject has been acquired accidentally. A physician is investigating a certain train of symptoms and he casually glimpses something he had not been looking for; or some concomitant condition at which he had not been especially directing his efforts, is cleared up and a new therapeutic procedure is born. Such experiences have laid the foundation for practical organotherapy, and while this form of therapeutics is often altogether empirical, we are or should be thankful that we can bring about results that are nothing short of marvelous, even though we cannot quite explain the "how" or the "why."

When the functions of the thyroid gland were just beginning to be appreciated some 25 years ago, most of those who studied the matter did so from

the standpoint of the influence upon the organism of the absence, either congenital or experimental, of this gland. A year or two later, when Murray, then of Newcastle, first administered a preparation of animal thyroids, he gave it to a woman suffering from myxedema, and for a long time thyroid therapy was confined to the serious major thyroid syndromes. Both these circumstances have tended to obscure the question of the less obvious thyroid disorders, and for a long time the use of this new remedy was limited to the treatment of those cases in which there was a marked affection or entire absence of the organ.

An important result of this still persists. Until quite recently the generally recommended dose of thyroid was altogether too large, at least, in the majority of the cases in which it is to be given. This was doubtless due to the fact that the original dosage as indicated in the various pharmacopeias was based upon experiences in the treatment of athyroidic individuals. It is true that a commonly suggested dose—five grains three times a day—may be none too much for myxedema or cretinism. Occasionally it may be increased advantageously above this figure, for in organotherapy “there is no dose save dose enough”—the only difficulty being how to determine when “enough” is given; but since we are now using thyroid in a host of other disorders related to functional minor hypothyroidism we must begin with much smaller doses, say

an average of one-quarter or one-half a grain three times a day.

This has had an unfortunate influence upon the practical consideration of this subject. Our attention having been directed to an important series of facts, we have overlooked much else that is of greater importance in every-day medicine. After all, the major thyroid insufficiencies are not so very common. We see them occasionally and usually they interest us only moderately, for the treatment is now fairly well understood and there is little to do save to follow the well-established procedures and supply the lack that nature or the surgeon accidentally has brought about. On the other hand the minor cases of hypothyroidism complicate the work of the general practitioner in such disorders as nocturnal enuresis, headache, cold feet and hands or chilblains. The dermatologist is concerned because of the connection of hypothyroidism with many dermatoses, such as psoriasis, prurigo, eczema or herpes. The internist finds a relation between this condition and certain forms of rheumatism and cardiac disorders. The neurologist knows that neurasthenia, melancholia, many forms of insanity and some of the psychoses may be purely thyroid in origin and as one prominent alienist once put it, "the most important single remedy in the asylum is probably thyroid extract." The gynecologist finds the thyroid a direct cause of many functional genital conditions and has learned

that it is so intimate with the ovaries that disorders of them cannot occur without some reflex influence upon thyroid activity, he also has found in thyroid extract a most useful means of treating many forms of female disease, especially amenorrhea and dysmenorrhea of certain forms. The surgeon finds the thyroid more of an unmitigated nuisance than a help, although a connection between thyroid activity and bone growth is reported and the control by this gland of development makes it of importance in the consideration of a number of deformities and dystrophies. Last, but not least, in pediatric practice thyroid therapy, and of course the physiologic influence of this gland, is all important; and thyroid extract is one of the most commonly used organo-therapeutic remedies in the treatment of many infantile disorders. We have already mentioned its possible utility in nocturnal enuresis; and in many nutritional disturbances, most of which are of endocrine origin, the thyroid is the most commonly disordered gland. In fact, one can hardly find a nutritional dyscrasia in children without very quickly tracing a part of its origin, at least, to the thyroid gland. Such manifestations as mental dullness, enlarged tonsils or adenoids, nasal or bronchial catarrh, dry, rough skin with coarse hair, as well as defective speech and occasionally soft bones, are all indications of a possibly deficient thyroid activity. The metabolic changes in rickets and marasmus are undoubtedly

partially due to disturbances in what Gauthier calls "the thyroid apparatus," i. e., the thyroid, thymus and parathyroids; and it seems quite certain that the idea that this disease was due solely to faulty feeding or to the impossibility of breast feeding, must now be relegated to the background and the thyroid and associated glands be given first consideration. It is quite remarkable how very small doses of thyroid—one-twentieth to one-quarter grain three or four times a day for some weeks—will modify many of the manifestations just mentioned—in adults as well as children. It is quite safe to say that the physician who remembers the extreme intimacy of the thyroid gland with disturbances of nutrition will be much more successful in their treatment.

Apropos of this, an interesting statement by Isabelle Thompson Smart of New York (Med. Rev. of Revs., 1915, p. 269) is worth quoting: "The subtle influence (of thyroid) upon the hormone balance regulates in a mysterious way the whole of the internal secretory activities. We cannot always explain why thyroid extract is such a remarkable remedy, but we are satisfied to know the extraordinary results that frequently follow its use where there is a metabolic disturbance of obscure origin and in which there are none of the indications of cretinism. An unscientific but very satisfactory means of treating this large class of cases is to give thyroid extract, as one physician says, 'like a hit

in the dark,' and while misses are not uncommon, the physician who does this will be surprised at their comparative infrequency."

When we recall the fact that the glands of internal secretion are inextricably related to one another and also that one cannot harm one without disturbing the harmonious interrelation of the others, the importance of this subject begins to grow upon us. Every-day circumstances such as the emotions, toxemia of alimentary and other origin, disease of all kinds, genital derangement of ever so slight a degree, especially in the female, and even the weather, may stimulate or depress, as the case may be, one or more of these hormone-producing organs with results which vary very decidedly in their clinical manifestations and seriousness.

I cannot refrain from making the briefest reference to a condition which has been aptly termed "the jerry-built constitution." The name is almost self-explanatory. By far the most important factor in such individuals is a thyroid instability. These individuals "catch everything," they are in a state of low metabolic activity, their urinary solids are low and the acidity is high. They are toxic. Neurasthenia is common in such cases. They are none too bright in their studies or their business. They are the skim-milk of humanity, and how much of it there seems to be. Study the internal secretory capacity of such individuals; enhance the action of

the thyroid, at the same time neutralizing the tendency toward acidemia and clean out the bowels, and there will be a metamorphosis that is sometimes astonishing. Right here I want to say that the treatment mentioned exclusive of organotherapy is by no means so efficient and I have come to the conclusion that the hormones really do the work and the re-establishment of a normal alkalinity of the blood and the removal of as many of the toxic products as possible merely puts Nature in a position to respond to the stimuli to which she is accustomed and the lack of which is such a potent factor in the etiology of many of the cases mentioned. The detoxicating procedures are negative treatment, if I may so term it; while the organotherapy is positive treatment. The former is good, for it gives Nature a chance; but both are better, because the hormones thus administered give Nature a boost.

You realize, of course, that we cannot begin to consider the whole gamut of minor thyroid disorders to-night. Their ramifications extend into every phase of medicine. Leopold Levi and Baron Henri de Rothschild, of Paris, have written two fairly large books on this single subject; and in their most recent publication the relation of the thyroid to each of the important disorders, acute and chronic, is thoroughly discussed. Many disorders which we have mentioned incidentally are given the prominence of a chapter to themselves.

But before closing I would like to lend a little more emphasis to some points regarding diagnosis, as well as to the administration and dosage of thyroid extract.

The diagnosis of minor hypothyroidism is comparatively simple. Most often, I must admit, it is presumed to be present and "diagnosed" by the therapeutic test. Several of the commonest symptoms have already been mentioned and for convenience it may be well to quote from a recent monograph by Lewellys F. Barker, of Baltimore, entitled "Some of the Commoner Types of Diseases of the Endocrine Glands":

In examining children for minor hypothyroidism, three principal points should be kept in mind: (1) retarded growth; (2) habitual constipation, and (3) dullness in the schoolroom. In adults the most important symptoms are (1) endogenous obesity; (2) persistent constipation; (3) a dry, harsh skin; (4) subjective feelings of cold, and (5) recurring drowsiness in the daytime. Barker advises the therapeutic test in all cases where there is any doubt of the presence of a condition of this nature; in other words, this eminent internist suggests recourse to empiricism, and he undoubtedly is right.

Some other symptoms which have directed attention to a thyroid insufficiency which had been entirely overlooked, may be mentioned. They are, however, not infallible signs: Cracked and brittle

finger nails; loss of the outer third of the eyebrows; twitching or blinking of the eyelids; fleeting and indefinite joint pains; low total solids in the urine; sensitiveness to cold and especially the need for an unduly large quantity of bedclothes; snoring (without other good reasons therefor); reduced resistance to infections, especially of the skin, as acne, etc. To these must be added the well-known symptoms of major hypothyroidism, though, of course, in the "minor" cases they are not so well marked.

Thyroid extract is a most useful remedy and like most drugs of its importance is worthy of much more study and far greater clinical application. Small dosage is always the rule. A quarter of a grain is my usual initial dose. It may be repeated from two to six times a day. Rarely is it necessary to give more than three grains a day in divided dosage. Occasionally one meets a patient who needs thyroid but cannot tolerate it; in such cases it is well to try giving the whole day's dose, not more than one-half grain at first, increasing later to one and one-half or two grains, at bedtime. This obviates some of the inconveniences with the heart and respiration. In this class of cases Heinrich Stern, of New York, gives sodium cacodylate in small doses with the thyroid. He finds that this mitigates the inconveniences of an idiosyncrasy to this remedy.

Thyroid must be given for some time to be most

effective. The French method appeals to me most. They give, say, one centigram (one and one-half grains) of thyroid per day, divided into three or more doses, and continue thus for one week. The drug is then omitted for a week or even longer, and then begun again for another period of a week, using the same or a slightly larger dose, then omitting it for another week or more, and so on. Occasionally individuals supersensitive to thyroid medication may establish a tolerance to a given dose, and after reducing the amount and starting again, it may be found that they are able to take very much larger doses with none of the previous symptoms of intolerance.

In many cases where thyroid is indicated, especially in obese women who are taking thyroid to facilitate reduction, pluriglandular therapy may be helpful. Corpus luteum given with the thyroid is sometimes of much assistance, especially in neurasthenic women and those at or near the menopause. In asthenic cases with a considerable degree of muscular weakness and constipation pituitary is given in conjunction with thyroid with good results.

Pituitary (whole gland) is often given advantageously with thyroid in children who have hypothyroidism. This is especially so in cases with mal-development and dullness. The dose may consist of one-quarter to one-half grain with half as much thyroid three or four times a day. The amount of

pituitary may be increased more frequently than the thyroid, giving finally, say, two and one-half or more grains of pituitary and one-half grain of thyroid at a dose.

An important point regarding the dosage of thyroid in children is the fact that the amount given is not regulated by the body weight or age of the child. Dosage depends solely upon individual susceptibility. The only way to establish a suitable dose for a given case is to start with a small dose, say, one-tenth or even one-twentieth of a grain at the usual intervals, giving increased doses very carefully until evidences of intolerance are noted. Then stop the medication for a period and recommence again with the previous dose or slightly less.

An important point to which I have never seen attention drawn concerns the label-dosage of several thyroid preparations on the market. Preparations of this character are usually given in tablet form, as it is most convenient and quite satisfactory. Manufacturers indicate the contents of their tablets in three ways on the labels: (1) 5-grain tablets; (2) 5-grain tablets, each tablet representing 3 grains of desiccated thyroid substance, and (3) tablets representing 5 grains of fresh thyroid glands. These figures are mentioned merely for convenience, since 5-grain tablets of thyroid are not used so much these days. It will be clear that (1) does not contain 5 grains of the active remedy of thyroid with no excipient to bind it or to facili-

tate its rapid disintegration. I much prefer the second way of expression; the size of the tablet is merely for manufacturing convenience and the amount of active constituent is definitely stated. Regarding (3) I cannot understand why a firm should insist on denoting the amount of fresh substance, rather than the standard (U. S. P., in this particular instance) preparation of dried gland. This may be the cause of trouble. For instance: A physician is giving a Parke, Davis & Co. tablet, 5 grains at a (hypothetical) dose. For some reason or another the treatment is continued with a Burroughs, Wellcome & Co. tabloid, but it is not noticed that "Tabloid Thyroid Gland Gr. 5" represents fresh substance, or only one-fifth as much of the dried gland as had been previously given! To reverse this experience would be much worse, for then a change of brand would entail a sudden multiplication of the desired dose by five! Parenthetically it may be remarked that this last-mentioned firm puts a "Tabloid Thyroid Gland Gr. 1-10," which contains only one-fiftieth of a grain of the dried gland.

There is a good deal more, but it will have to be left for another time. Suffice it to say that minor thyroid insufficiencies are as common in the average run of patients as orange trees are here, only they are not always so obvious.

Let us cultivate our sense of discernment so that cases of this kind will not slip by unnoticed again.

# V

## PLURIGLANDULAR INSUFFICIENCY: ITS INCIDENCE AND TREATMENT

PLURIGLANDULAR insufficiency, or hypo-endocrinism, is a comparatively recent term, rarely found in the medical literature published seven or more years ago. To appreciate the full import of the subject which has been allotted to me, it is necessary, first, to realize the fact that the endocrine system is a very essential part of the organism, since by its various internal secretions practically the whole of the workings of the body are regulated and correlated. It might be compared to the magneto of the automobile or, perhaps, to the exchange of a telephone system.

In his comment in the New York Medical Journal (1) on the advanced position taken by a Committee appointed by the Congresso della Societa Medica Italiana in 1912, the editor says: "One cannot but be impressed by the vast field which the ductless glands have steadily invaded, in keeping with the conclusions announced nearly ten years ago, in this country, that these organs were second to none in the body in their bearing upon physiology, pathology, and clinical medicine." The Committee representing these Italian investigators in their official report to the Congress (2) asserted

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that: "The internal secretions manifest an influence upon the anomalies of growth, morphology, and organic metabolism; on nutrition and inherent excitability of the nervous system; on resistance to infections and intoxications, as well as a preponderating role in the causation of dyscrasias and morbid temperaments." They also conclude that the equilibrium of the nervous system, the sympathetic in particular, may be regarded as maintained by the internal secretions and that in nervous diseases per se they act probably as indirect or predisposing factors.

The active principles of these internal secretions are now generally called hormones, and we are beginning to realize that they are a factor of extreme importance in the regulation of metabolism. In the body every motive force is balanced by a retarding force and this nice balance is essential to health; hence if one or another of these factors gain the ascendancy, or is diminished in activity, disorganization must naturally result and the extent of this disorganization can hardly be confined to the single area in which it is initiated.

The intimate relations of the secretions of the various endocrine organs predicate pluriglandular disturbance as the result of an initial monoglandular disorder, thus explaining the dictum of Bayard Holmes (3): "During the past year much evidence has accumulated to show that diseases of the ductless glands are usually plural rather than isolated

and single. Pluriglandular disease is the rule rather than the exception."

This position is substantiated by Mullaly (4), who states that from a study of the autopsy records at the Royal Victoria Hospital, Montreal, "In the infrequent autopsies in cases of ductless gland disorders pathological changes were observed in more than one of the ductless glands."

Functional disorders of many varieties may be either directly due to, or intimately associated with, changes in the various hormone stimuli which are so essential to the maintenance of the chemical balance upon which the intricacies of metabolism depend. Many of these disorders are already included in our present-day classification of disease and are considered among the "disorders of the internal secretory glands"; in most of these cases, however, the disturbance is prominent in one of the glands, and among these we recall thyroid insufficiency, the major form or myxedema and the minor form, sometimes known as Hertoghe's syndrome (myxedeme fruste), adrenal insufficiency or Addison's disease, Langerhansian insufficiency or pancreatic diabetes, parathyroid insufficiency or tetany, and numerous other disorders of function resulting from disturbance in the internal secretory activities of the gonads, hypophysis, epiphysis, etc.

Harry Campbell, in his masterly study of the role of the blood plasma (5) rightly intimates that the blood plasma carries a host of varying chemical

messengers or hormones whose balance is essential to the proper regulation of the numerous bodily functions. This explains why the normal content of the chromaffin principle does not exert the same action as when a dose of adrenalin is administered—in the normal amounts in which it is found in the blood it is balanced by the Langerhansian principle.

Campbell considers that cell activity is properly divided into the egoistic and the altruistic cell functions. The former consists in the maintenance of individual cell activity, while the latter concerns the supply to the organism as a whole of certain services, probably brought about by the hormones, such as are exemplified in the numerous functional relationships between organs. This so-called "altruistic" function is of extreme importance, for the cell itself may seem to all intents and purposes quite healthy and yet still gravely fail in its altruistic functioning—a failure which, small though it be, may suffice to disorganize the delicate hormonic balance. A consideration of these complex interrelations\* will establish the extreme importance of the hormone equilibrium, and, of course, its disturbances.

There are two forms of endocrine disorder—organic and functional. The former, fortunately rare,

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\*For a fuller discussion of this question, see Chapter III, "The Hormone Balance," in *Practical Hormone Therapy* (Bailière), by the writer of this article.

is usually diagnosed only when the changes are permanent; it is, therefore, very difficult to treat satisfactorily. The latter, on the other hand, is extremely common, it is frequently overlooked, and, when its presence is appreciated and put under treatment, it responds in an encouraging way. Hence the principal effort of the writer will be to emphasize the frequency and importance of functional insufficiencies of the endocrine organs, rather than the definite organic diseases of these glands. One can, however, advantageously refer, in passing, to several important papers and case reports which outline the pathology of those serious organic conditions which combine to form the "pluriglandular syndrome."

One of the most pronounced cases of organic pluriglandular disease was recently reported by Maase, (6) the essential facts being briefly recapitulated here: The patient was a Russian girl aged 24, with an epileptic and diabetic ancestry. Normal in every way till 18, she then developed ophthalmoplegia. At 20 she developed a myxedematous state attended by suppression of the menses. Glycosuria was found and a positive Wassermann reaction; later a spinal curvature was discovered. There was a shrinkage in the body measurements represented by various deformities. The bone condition somewhat resembled osteomalacia. Death occurred unexpectedly from erysipelas. At the autopsy the hypophysis, normal in size, was adherent to the

bone and of firm consistence. Thymus remains were quite abundant, while the thyroid was abnormally small in both lobes. The pancreas was small, consisting largely of fat and connective tissue. The ovaries were abnormally small and showed no Graafian follicles. The bones were much thinned and brittle, the liver was fatty. The adrenals alone of all the endocrine glands seemed to be normal, so that the case may be termed subtotal or hypo-endocrinism. The other organs were normal, save that the heart exhibited the changes to be expected after death from erysipelas.

In the Italian medical literature of the past year Consolazio, (7) Bianchi, (8) and Zilocchi (9) have contributed interesting monographs on this subject. In France, Costa (10) and Rebattu (11) have discussed this subject, and Parhon and his associates (12) have experimentally produced conditions in animals allied to the pluriglandular syndrome. All of these communications consider the serious organic conditions, and while there is undoubtedly advantage in studying this phase of the subject, it is of far less immediate practical value than the consideration of the much more frequent functional disturbances which, because of their insidious onset, frequently are entirely overlooked.

Costa (10) states that nice distinctions between conditions due to the various ductless gland disorders are very difficult to make, since the internal secretory glands all have an action on the develop-

ment of the skeleton, on nutrition, and also a pressor or depressor action on the circulation. He does not attempt the differentiation suggested by Claude and Gougerot, (13) Gandy, Deseglise, and others, to determine in which gland the hypofunction predominates and which is essentially responsible for the disturbance. This undertaking appears to him much too difficult at present. In Costa's case, however, the discovery of the cause was made by the Wassermann test and antisyphilitic treatment caused a marked change for the better.

The majority of the serious organic disturbances of the ductless glands seem to be syphilitic in origin. The case reported by Costa above was luetic. In Maase's case, which has already been quoted, there was a positive Wassermann reaction, and de Moraes and Pernambuco, (14) in considering the relation of the pluriglandular syndrome associated with dementia precox in a girl of 19, established the cause as inherited syphilis. They found that the ovaries, thyroid, adrenals and mammae were simultaneously affected.

The only reason that we study disease is that we may be able the better to appreciate its influence and satisfactorily treat it, so the consideration of pluriglandular insufficiency would be incomplete without reference to the treatment of these conditions.

The natural corollary of pluriglandular insufficiency is pluriglandular therapy, and the most

practical consideration of this subject concerns the comparatively recent form of therapeutics which the knowledge of the influence of hypoendocrinism has made possible.

It is altogether possible that the change of air ordinarily recommended to convalescents and invalids, sanatorium treatment and other hygienic regimens, are beneficial largely because of the increased activity of the secretory capacity of all the glandular organs and it seems that the tonic physical measures, such as hydrotherapy, electricity, massage, etc., are useful in part at least because they stimulate the endocrine organs to produce their vital messengers. In fact, Nogier (15) has suggested a special line of treatment with the hope of specifically exciting the internal secretory organs by physical methods, just as these methods are used to stimulate other functions, thus materially modifying the conditions due to hypoendocrinism. This may be good, but to my mind cannot be compared with the more direct organo-therapeutic methods.

The most natural means to favor internal secretory activity are the products of the internal secretory glands themselves. Hallion's law is the fundamental basis of scientific organotherapy. It is as follows: "Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its

action, and, when it is injured, that it favors its restoration."

One of the most important statements on the hormones is found in Starling's monograph on "The Chemical Co-ordination of the Body Functions." (16) This eminent authority confidently states his belief that "if the mutual control of the body be largely determined by the production of definite chemical substances in the blood, the discovery of the nature of these substances must enable us to interpose at any desired place in these functions, and by this means to acquire an absolute control over the working of the human body. Such a control is the goal for which medical science must ever strive."

Possibly, the not infrequent cases of seeming monoglandular disorder which do not respond to the orthodox treatment whether organo-therapeutic or otherwise, might be more responsive to our therapeutic efforts if the fact that pluriglandular disease is much more common than monoglandular disease was considered, and the administration of suitably combined extracts was substituted for the present thyroid, pituitary, adrenal, ovarian or other single extracts which may seem to be the proper treatment.

It is quite certain that this subject, now on the verge of our present knowledge, before many years have passed will be taken into careful consideration by the general practitioner as well as the

internist, and the hormone balance will be a factor which is more thoroughly appreciated. It is true that the goal referred to in Starling's quotation is still far distant, and we are a long way from acquiring "absolute control over the working of the human body," but there can be no reasonable denying that the administration of certain organic extracts makes possible a control over certain functional conditions that is not obtainable in any other way.

For several years the writer has been studying the applications of various combinations of pluriglandular extracts in pluriglandular insufficiencies, particularly in the so-called "run-down" conditions, where no easily demonstrated and positive evidence of any defective action of a gland or series of glands can be demonstrated. Such cases include many forms of neurasthenia and functional neuroses, and it is obvious that in the majority of these cases there must be a disturbed endocrinism. It is hardly reasonable to suppose that in an individual with prominent manifestations of half-speed function, such as constant fatigue on slight exertion, defective oxidation as evidenced by low urinary solids, nerves that are easily set "on edge," circulation that is poor, with cold, clammy extremities, and not infrequently reduced tension and ambition, and mental powers much below par, that the production of the essential chemical messengers is not reduced just as are all the body activities. This

being the case, pluriglandular therapy not only serves to replace, in however slight degree, the missing secretions, but favors an increased production of them by the homostimulant action already referred to.

Theoretically this sounds very plausible and practically it has been found to work very nicely. Pluriglandular therapy is undoubtedly empirical, for in the class of cases under discussion at least, there is no definite proof as to which of the ductless glands is deficient and to what extent. For this reason it has been ridiculed by some who forget that nine-tenths of our present therapeutics was at one time purely empirical, while a good share of it still has no positive scientific basis. A procedure that has secured results before may do so again, hence it is worth trying. This is the present position of pluriglandular therapy, and it is believed that the successes already obtained are an earnest of what is in prospect.

Several combinations of organic extracts have been tried experimentally, and from a considerable experience it seems that the really tonic principles of this character are to be secured from the pituitary body, thyroid and gonads. My experience has been limited to the use of combinations of the extracts of the ductless glands which are known to have a tonic effect. Chief among these are the thyroid, posterior lobe of the pituitary and gonads, and for the past two years I have used a preparation

called hormotone with excellent results in a variety of "run-down" states, in some of which there were obvious disturbances of one or more of the ductless glands and in others in which this change was presumed to be present though not so evident from a clinical standpoint.

Leonard Williams, whose studies in this field are of considerable interest, reported to the therapeutical section of the Royal Society of Medicine (17) that he had found that while pituitary substance had given good results in those "curious and indefinite conditions—neurotic or neurasthenic—which occur so frequently in moth-eaten maiden ladies who emerge from boarding houses to go to church—I do not know how it does it, but it makes them feel better. . . . Since I have been using a mitrailleuse called hormotone I have had considerable success in those cases just referred to as benefited by pituitary." Among the conditions which I have treated are neurasthenia (in men and women), amenorrhea, sexual neuroses and impotence, as well as several cases in which the manifestations were not sufficiently marked to be definitely named—the "run-down" conditions.

This treatment is by no means a specific, and my percentage of good results is only between 60 per cent. and 70 per cent. I have seen no really bad effects, the only untoward effects occasionally noted being a feeling of irritability and temporarily increased nervousness, which disappeared on re-

ducing the dose of hormotone and did not reappear when its administration was very gradually increased.

In senile conditions and old age there is an invariable pluriglandular insufficiency due to the progressive decline in all the functions. Lorand, whose book on this subject (18) is practical as well as interesting, makes frequent reference to the value of organotherapy, and I must admit that, in a number of cases which have come to my attention, the combination previously referred to has seemed to rekindle the vital fires.

The advantages of pluriglandular therapy are essentially the advantages to be derived from the individual substances which are combined. Obviously such combinations are made with their synergistic action in mind. I have personally used small doses of antagonizing extracts with good results, because it seems that each of the substances stimulates the corresponding organs, thus increasing the hormone content of the blood as a whole and strengthening the chemical messages which are of such vital importance. A point worth emphasis concerns the capacity of the individual organ to respond to the stimulus of the corresponding extract. It seems established that "the degree of stimulation exerted by the administration of the hormone-bearing substances is in direct ratio to the need for such stimulation, i. e., an extract is more efficient when a corresponding active principle is deficient in the

body than when present in normal amounts. Hence in a combination of several extracts the principal action is the one which is deficient; that is to say, the more it is needed, the more useful it is." (19)

Before closing it is proper to mention several reports in the literature on various forms of pluri-glandular therapy. In addition to the treatment of the definite thyro-pituitary deficiencies with thyrodi and pituitary extracts, as first suggested by Renon and Delille, (20) Starkey (21) has been treating certain nervous diseases with a combination of thyroid, parathyroid, testis and ovary.

In gynecological practice it is not uncommon to combine lutein with small doses of thyroid with advantage in conditions where lutein may be indicated. A combination of several extracts is given by McCready in children with defective endocrine development and it seems quite well established that combinations are more useful than single gland extracts—at least in this class of cases.

Bazzochi (22) has used a combination of thyroid, thymus and spleen in pyloric cancer. In pharyngeal carcinoma, Shirlaw (23) suggests the use of the preparation called "Tabloid three glands," each tablet containing a large dose of thyroid (6 grains) with the addition of small doses of adrenal and pituitary substances. Unquestionably in cancer there is a definite hypoendocrinism, and attempts to modify this, while possibly without specific effect upon the cancer itself, may be of assistance in

modifying other conditions which cause inconvenience to the patient. "Cancer is essentially a disease of nutrition—i. e., errors in nutrition, whether local or general, are the factors which permit of the implantation of cancer cells and the growth of the tumor. The ductless glands preside over nutrition. Hence it is not unreasonable to suppose that there may be some relation between disturbances of the hormone balance and cancer, and, too, that there may be some prospect of therapeutic value in the treatment of this disease by organotherapy." (24) Finally, Billard (25) has advocated a combination of the extracts of spleen, liver and pancreas as an adjunct remedy of possible helpfulness in cancer.

Altogether the possibilities of various pluri-glandular combinations are almost without number, since, as Leonard Williams (17) has indicated, the mitrailleuse is seemingly more useful than the single rifle shot.

Since this was written Little (26) has made another interesting communication on his study of cancer, and shows that not only must we consider the relation of the ductless glands and their disorders to cancer, but that the use of certain products of these organs has a decided effect in favoring the response of the body to other treatment. He used extracts of the pancreas and adrenal cortex. Little's hypothesis has several important points which are worthy of repetition: The prob-

able origin of the growth is in a highly specialized cell or cells, which for some reason or other have undergone a retrograde metamorphosis to the point where the power of reproduction, common originally to all cells but lost in these highly specialized cells, has reappeared. This reproduction of such reverted cells is caused by a relative hypo-function of certain ductless glands. The ductless glands at fault in each case have some vital relation to sugar metabolism or calcium metabolism or both.

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It is over two years and a half since the foregoing was prepared, and in that time I have had numerous opportunities to see how important is the appreciation of pluriglandular conditions. Nothing establishes one's faith in medicine, or any part of it, like clinical success. So I will amplify this chapter with two brief case reports, one with which I had to do personally and the other to which my attention was drawn by the late Dr. Wendell Reber of Philadelphia.

When my address was given before the Riverside County Medical Society\* Dr. D. C. Strong of San Bernardino, reported a case of pituitary cyst in a boy. This had been successfully punctured and decompressed and the boy recovered from the neighborhood and pressure symptoms and was given pituitary gland with additional improvement. How-

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\*See Chapter IV.

ever this did not last, and the lad's mentality and progress was about at a standstill when I heard of the circumstances. Naturally defective mentality reminds one of thyroid trouble, despite the proven pituitary disease, and I suggested that the pituitary feeding be continued and reinforced with the addition of thyroid gland. This was done with astounding results, for the boy is now as bright as any of his schoolmates and an excellent student. Here, of course, the pituitary insufficiency was but a part of the complex, and the pluriglandular therapy was much more successful than the administration of the single gland alone.

The other case was just as peculiar. Dr. Reber wrote me of this and has since reported the case in the New York Medical Journal (1915, ci, 392). A man came for treatment for a progressive blindness and for some reason or another was given thyroid gland with no perceptible benefit. He then received pituitary gland in conjunction with the thyroid, with considerable benefit to his vision. Some time later the vision was again impaired and pituitary gland was given since it had been so effective previously. It was a failure until it was recalled that he had taken both thyroid and pituitary, and thyroid was added. The benefit was as prompt as previously, thus giving fairly substantial evidence that thyroid alone and pituitary alone were practically inactive; but that the combination caused a change in conditions which allowed of a

re-establishment of the disorder under treatment.

I am confident from many clinical experiences that cases in which, say, thyroid treatment is obviously indicated, often will respond more satisfactorily when further search is made for associated endocrine disorder and suitable pluriglandular medication is substituted.

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## VI

### SHELL SHOCK ("NEURASTHENIA") AND THE INTERNAL SECRETIONS: WITH SUGGESTIONS AS TO TREATMENT

THERE seems to be reliable evidence, both physiological and clinical, that the severe nervous disorganization not infrequently following a period of trench warfare, is either directly due to a disturbance in the work the glands of internal secretion, or at least is complicated by a glandular dyscrasia or dyshormonism (dyscrinism).

The writer has had no opportunity to see cases of this character, but several reports from correspondents on war service have aroused an interest in this subject, which has lead to a study of its literature and a comparison of this with the writer's personal observations.

The excellent work of T. R. Elliott, (1) of London, followed by the comprehensive series of experiments by Cannon, (2) of Harvard, has quite definitely determined a relation between the adrenal system and the sympathetic nervous system. It is now understood that those factors which act upon and through the sympathetic nervous system

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NOTE: The editor of "The Prescriber," who is a personal friend of the writer, submitted certain clinical notes and suggestions, and at the same time asked for an article outlining some sort of a feasible explanation of the possible relation of the endocrine glands to shell shock. This is merely an attempt to relate these.

also influence the adrenals; and that the sympathetic manifestations resulting from pain, rage, fear, hunger, and the emotions cause a decided stimulation of the adrenals with an immediate production of a greatly augmented supply of adrenin to the circulating blood. This is followed, at a longer or shorter period, by an equally well defined adrenal depletion or hypoadrenia, accompanied by just such clinical manifestations as we expect to find in shock—vasomotor irritability and instability, hypotension, insomnia, depression, and an extremely well marked asthenia. This last symptom is the typical accompaniment of adrenal disease (Addison), and almost invariably complicates the syndrome of pluriglandular insufficiency (hypocrinism).

This condition of hypoadrenia is not uncommon in consulting work, and complicates many more cases than one might expect. Crile's "anoci-association" is nothing more nor less than an attempt to forestall just such a condition by the removal as far as possible of circumstances known to cause adrenal excitation prior to operation. Sajous has long emphasized the importance of "terminal hypoadrenia," while Sergent, of Paris, has written many an article upon "*l'insuffisance surrenale.*" These contributions more than convince one that this endocrine syndrome is quite common.

Judging from the foregoing physiological facts, "one can quite easily understand that just such a

condition would be present in individuals driven from home and subjected to exposure and hunger. Similarly, men returning from the trenches, where they have been subject to extreme fatigue and the tenseness of the atmosphere, as well as the mental effects of losing their comrades and themselves suffering from wounds and shocks, must also be considered to be in a state of adrenal insufficiency." (3) This condition of hypoadrenia was a prominent factor in the "vivisection of a nation," so well explained by Crile in an address delivered at the American Ambulance at Neuilly, during his service in France. (4)

Elliot Smith, (5) of Manchester, after carefully considering the incidence and causation of shock in soldiers, intimates that mental instability is the most common groundwork for the superimposition of this condition. His position may be summed up in his own words: "The real trauma is psychical, not physical." While it is impossible to deny that the impressions upon the mind are both decided and influential, there must also be a physical factor in many of these cases.

This subject was recently referred to by Renon (6) in a paper read before the Societe de Therapeutique, Paris, and the symptom complex which he describes as due to l'angoisse de guerre is almost typical of dyshormonism, and especially that form in which hypoadrenia is well marked. Renon finds

that a neuropathic or arthropathic physical substratum is common in individuals subject to the more marked effects of "war shock," and that the use of alcohol is a pronounced predisposing factor.

Among the usual symptoms enumerated by Renon as being due to this "war neurasthenia" are several which can be quickly connected with the endocrine organs. A progressive loss of weight is the rule—the glands of internal secretion control both nutrition and growth; the temperament is changed and the disposition becomes uncertain—mental stability and activity are commonly connected with ductless glandular dyscrasias; arterial tension is reduced—common both in pluriglandular insufficiency and in hypoadrenia; dermography is reported to be nearly always present—one of the typical manifestations of severe adrenal depletion is the dermatographic sign first mentioned by Sergent, and called by him *la ligne blanche surrenale*. I cannot but believe that the most constant single factor, and one that is quite susceptible to treatment, in "shell shock" or "war neurasthenia," is pluriglandular insufficiency.

That this conception of the relation of neurasthenia to the internal secretions is coming to be more generally accepted may be noted from a recent editorial in the Journal of the American Medical Association, (7) which comments favorably upon a paper by T. A. Williams, (8) of Washington, describing the disorder as a syndrome of ad-

renal insufficiency. Williams very aptly remarks that the term "neurasthenia" is only a "convenient cloak for failure to investigate the case sufficiently," and that there must be some tangible cause. He concludes that many patients who show symptoms of neurasthenia with low blood pressure, loss of mental elasticity, mental and physical depression, and who tell of having "lost their nerve," are very frequently suffering from adrenal insufficiency. He has given dried adrenal substance in such cases, and has noted improvement in many of them.

Corbett, of Minneapolis, (9) finds that adrenin insufficiency is a prominent factor in shock; he does not maintain that its loss is shock, but rather that adrenin is necessary to overcome shock, and any factors which deplete its supply favor the development of that condition. Symptoms of shock fully develop only after the adrenals are greatly exhausted, and symptoms of it become extreme the more marked is this adrenal depletion. He concludes that shock is a composite in which adrenin exhaustion and oligemia are predominant factors. Anesthesia, pain, fright, and trauma are immediate agents in producing adrenin exhaustion as well as shock.

Sir James Mackenzie (10) asserts his belief that at least 90 per cent. of the cases of "soldier's heart" that have been certified and treated as cardiac affections are not primarily heart cases at all, and that the principles of treatment applicable in such cases

differ widely from those for the control of heart failure. The symptoms enumerated by Mackenzie are quite similar to those mentioned previously as being expected to follow hypocrinism and, especially, severe adrenal exhaustion. He mentions a sense of fatigue or exhaustion easily induced as being common to all—the typical “endocrine asthenia” already noted several times. The heart’s rate is often not increased, but in some it is persistently increased, as high as 120 per minute—a condition commonly associated with dysthyroidism. The mental condition is somewhat varied, periods of depression are not infrequent, and patients are often very irritable—both connected with dysthyroidism or, still more commonly, with dyscrinism.

Mackenzie urges that the main principles of treatment of this heart disturbance should be devoted to increasing the health of the body as a whole, so as to increase the natural resistance to infection, to eliminate toxic influences, and to brace up the whole man bodily and mentally. To achieve this, Mackenzie recommends fresh air and judicious exercise. While these are doubtless most important measures, it must be remembered that resistance to infection is largely the concern of the thyroid gland, while the principal detoxicating agencies in the body are the liver, the thyroid, and the adrenals. In the matter of treatment, therefore, it is only rational that these organs should be studied and, where advisable, suitably stimulated.

From what has preceded it will appear that medication calculated to stimulate the adrenal system may be helpful in cases of shell shock or neurasthenia; and doubtless it is, especially if used in the manner suggested by Tom Williams, i. e., desiccated adrenal gland by mouth. Sergent has been using this form of treatment in France, (11) and finds it of exceptional value in the severe cases where the signs of acute adrenal exhaustion are elicited. Here hypodermic injections of adrenalin solution, from 15 to as high as 30 minims at suitable intervals, have undoubtedly saved life.

In the course of the discussion of Corbett's paper, (9) mentioned previously, one physician asked why, if these symptoms are due to adrenal insufficiency, cannot they be relieved by the administration of adrenalin. In his reply Corbett said he did not think that adrenalin, administered artificially, was the antidote for shock, because the amounts of adrenalin normally in the blood are exceedingly small, and if an attempt were made to maintain the blood pressure by forcing adrenalin, continued larger doses would have to be used to maintain the results. Such continued and increasing dosage would have a deleterious effect upon the blood vessels, and might increase the concentration of the blood, adding this factor to the shock. I am not sure about this effect of adrenalin on the vessels, but I do know that pituitary preparations are much more effective than adrenalin in the immedi-

ate treatment of shock and collapse, their influence is more prolonged, untoward by-effects, as rigors, coldness, palpitation, etc., are less likely to follow, and the general influence upon other functions, as diuresis, intestinal peristalsis, etc., are both salutary and desirable. Hence recourse to posterior pituitary preparations is now almost the rule in the immediate treatment of shock, though there are undoubtedly cases of severe hypoadrenia, such as those mentioned by Sergent, Sajous, Josue and others, in which a dose of adrenalin might give better results.

The use of one or the other of these hormone preparations in cases of this character is rational; but they are not quite suitable measures for the control of the chronic, unyielding, and persistent syndromes which outlast the actual collapse, and we must look elsewhere for help.

Fortunately we have other endocrine glands which are so intimate with the adrenals as to be classified by some as a part of the "adrenal system," and from them we can draw in the hope of gaining results in this class of disorders. The thyroid, pituitary, and gonads all contain principles that are valuable here. Combinations of these have been used for some years with good results. The marked advantage of pituitary, for instance, over adrenal substance is that it contains a more stable and therapeutically lasting principle, and, without going into details, its influence upon the vascular and

muscular tone seems to be much better than that resulting from adrenal therapy.

The stimulating effect of small doses of thyroid extract is not confined to cases with obvious hypothyroidism. As a matter of fact, this influence upon the adrenals is well marked. Sajous, Schafer, and others have directed attention to the close histological and physiological analogy which exists between the interstitial cells of the gonads and the corresponding cells in the adrenals. There seems to be a rational as well as an empirical basis for pluriglandular therapy; for one is thus following Nature's own method by giving a mixture of several useful principles.\* Further than this, the various cell units of the body have accustomed themselves to selecting those chemical messengers which they stand most in need of (the blood is a solution of unnumbered chemical substances); consequently, when we give several organo-therapeutic extracts combined, the influence that may be expected to predominate is the result of the action of that hormone which is most needed, and for which certain cells are seeking in vain, simply because the organ producing it has been played out.

Another reason for giving mixed gland extracts lies in the fact that all these endocrine organs are so intimate with one another that disturbance in one invariably causes changes in the work of the

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\*Just as we use combinations of the four food elements and expect the body to make use of each where it is needed most.

other glands upon which the first affected gland is dependent. According to Bayard Holmes, (12) of Chicago, evidence has accumulated to show that disease of the ductless glands is usually plural rather than isolated and single. "Pluriglandular disease is rather the rule than the exception—the use of gland extracts in the treatment of aplasias of the pluriglandular system has become an established therapeutic measure of miraculous potency."

From a clinical standpoint I have had occasion to use a preparation called Hormotone in a number of cases "knocked out" by combinations of circumstances other than those related to trench warfare. I have found it useful in various forms of neuroses due to toxemia or severe mental strain, and in several of the gynecological troubles in which there is a well defined dyshormonism. This preparation contains the so-called "dynamogenic" hormones from the glands which exert their principal effects on the adrenal system: these are the thyroid, pituitary, and gonads. Small doses of these extracts are useful in the adjunct treatment of just such cases as have been outlined in this article. I have had several most interesting experiences reported to me from Europe, and since they will form a fitting climax to this communication, a resume of them will be given.

At a hospital in —— five cases of "trench neurasthenia" were treated for some weeks with from  $2\frac{1}{2}$  to  $7\frac{1}{2}$  grains of this preparation three times a

day, in addition, of course, to the usual expectant treatment. Their wounds had all healed, but the shock was still prominent, and tachycardia, tremors, and depression were present. All suffered more or less from insomnia. Two weeks of this treatment enabled two to be discharged "fit for service," despite the fact that they had been under treatment "for weeks and months with no perceptible improvement." The other three grew better, but did not respond so rapidly.

Another report mentions the use of this preparation in several soldiers home from the Dardanelles with the usual after-effects of severe dysentery and nervous shock. (By the way, it has been well established that dysentery is a most common cause of hypoadrenia, while some believe that the algid stage of this disease, and of cholera, is essentially an acute adrenal exhaustion.) Hormotone evidently assisted in the re-establishment of the normal "balance," the appetite increased, and it was possible for these soldiers to sleep quietly and restfully. It was also remarked that they lost the feeling of depression, which, after all, is one of the most serious and persistent of the symptoms of this disorder.

In France the practice of "opotherapie" has reached a much more advanced stage than in England or America. Pluriglandular therapy is fairly well established there, and there should be no reason why the results could not be duplicated any-

where. In Germany, too, this subject has not been overlooked, although the German literature has always evidenced a paucity of information on organotherapy, most of the real advances in this line having emanated from other countries. Thyroid was introduced by George Murray, of Manchester; pituitary medication by Blair Bell, of Liverpool; parathyroid treatment by Vassale, of Turin, and Berkeley, of New York; adrenalin, as all know, originated in the investigations of Aldrich and Takamine; the corpus luteum was first studied in France; Brown-Sequard, of Paris, is the "father of scientific organo-therapy"; hepatic opotherapy was first used by Gilbert and Carnot, of Paris, etc. The only reference to this subject in recent German literature is that of Kohnstamm, (13) who relates a number of instances in which thyroid, hypophysis, or adrenal preparations were used to improve the morbid conditions resulting from disturbances in the internal secretions caused by the emotional strain of the soldier's life while on active service.

I believe that the systematic administration of pluriglandular extracts opens up a new era in organotherapy. As an adjunct to other indicated treatment it favors the restoration of the disturbed "hormone balance," so well discussed by Harry Campbell, (14) and others. The theoretical side of this subject is outlined quite fully in my book, (15) and since its publication I have had many opportunities to test its efficacy in civil practice. I be-

lieve that it will be just as efficacious in the treatment of soldiers, and that the results already secured are a pleasant foretaste of what may be expected by applying this suggestion much more extensively.

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Since the above was published it has come to my attention that the application of pluriglandular therapy in similar conditions both in this country and abroad is indeed an efficacious measure, even though the foregoing explanation may not be beyond discussion. One case in particular comes to mind: A man, previously in good health, went through a "near accident" but was not hurt. His blood pressure was 80 mm., his temperature was subnormal, his heart action hurried and he was obviously suffering from shock. Tonic organotherapy "acted like a charm" and by the thermometer, sphygmomanometer and stethoscope it seemed quite clear that a very tangible service had been rendered.

Another case of a somewhat similar nature was recently reported by Dr. Vanderwyst of Kansas. A girl of 17 had manifested a neurosis for five years following a severe experience with a cyclone when she was twelve years old. Since then her temperature has been very unstable, she suffered from various vasomotor disturbances and was subject to severe emotional "storms." She was much run down, anemic and suffered from transitory attacks of pain

in different parts of the body, especially in the spine.

After varied and protracted treatment she was given a course of pluriglandular therapy represented by the Roberts-Hawley Lymph with a very remarkable re-establishment of normal emotional and nervous stability as well as an accompanying gain in weight and health.

This is but an additional indication, to the writer at least, that the dynamic or antiasthenic effect of hormone therapy is deserving of consideration in the neurasthenic manifestations due to or akin to "shell shock."

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11. Sergent: *Bull. Acad. Med. Paris*, Sept. 7, 1915; see *Amer. Med.*, 1915, xxi, 922.
12. Holmes: *Lancet-Clinic*, 1914, cxiii, 705.
13. Kohnstamm: quoted in *Critic and Guide*, 1916, xix, 153.
14. Campbell: *Lancet*, 1907, i, 313 et seq.
15. Harrower: "Practical Hormone Therapy," *Bal-liere*, 1914.

## VII

### THE ADRENAL GLANDS AND THEIR SIGNIFICANCE IN GENERAL PRACTICE

THE study of the adrenal glands has received a great impetus since Cannon recently announced his epoch-making discoveries of the physiological changes in these glands dependent upon the emotions. The practical application of this new knowledge is important, though it is not yet appreciated as much as it deserves. Sometimes it takes a long time for the experiences of the physiologists in their laboratories to be translated into terms of every-day utility to the practicing physician; and in my somewhat broad association with physicians in different parts of the world, during which we have almost invariably discussed matters pertaining to the internal secretions, I have noticed quite a lack of appreciation of the clinical value of Cannon's work.

Briefly, we now know that the emotions, fear, rage and pain, stimulate the adrenal glands; and it is believed that many of the phenomena which usually accompany emotional strain, really result from the excessive amount of adrenin liberated from the adrenal medulla by the psychic stimuli; or from the glandular depletion which one would nat-

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Read by invitation before the Pasadena branch of the Los Angeles County Medical Association, and published in the Medical Review of Reviews (New York) May, 1917.

urally expect to follow excessive functional activity.

I am confident that if this fundamental physiological principle were kept in mind, and the connection between the adrenals and certain affections was understood, the appreciation of this usually overlooked element would make a good deal of difference to the diagnostics and the therapeutics of these conditions—would further revolutionize our conceptions of disease. It is for these reasons that I have chosen this subject for brief consideration to-night, and I am confident that much practical good can come from the clinical application of Cannon's remarkable experiments. To those who may become interested in the intricacies of this matter I warmly recommend Cannon's book, "Bodily Changes in Pain, Hunger, Fear and Rage,"\* in which the subject is considered from its experimental aspect. It is a fascinating book.

With these new principles in mind we can now begin to explain the sudden onset of serious symptoms and even diseases, following some severe mental shock. We can understand more thoroughly the comparatively recently discussed kinetic system, as well as what Crile pleases to call "anoci-association," both of which are intimately related with the function of the adrenal glands, especially as it is influenced by pain, mental stimuli and the

emotions. There is a much wider application of this than that which is being so successfully applied by Crile and his followers in their surgical work.

Let us first recall the physiological reactions which result from excessive or deficient adrenemia. An increased output of the chromaffin hormone, adrenin, favors the production of an increased sympathetico-tonus, increases the reactivity of the organism to all sorts of impressions, augments cardiac action, raises the arterial tension, hinders intestinal motility and causes a decrease in the functions of the pancreas, especially as regards its internal secretory capacity with possible glycosuria (clinically analogous to the experimental "adrenalin glycosuria" following injections of this substance, as well as to the "experimental pancreatic diabetes" which invariably follows removal of the islets of Langerhans).

On the other hand the chromaffin cells may be so unduly stimulated that they become transiently, or even permanently, played out; and a condition of adrenal insufficiency ensues, which is quite common in general practice as we will shortly see. This hypoadrenia is responsible for reduced sympathetic tone, lessened muscular excitability and capacity with exhaustion on slight exertion, or asthenia (quite the most prominent and constant symptom of this disturbance), reduced cardiac power and, sometimes, rate, lessened blood pressure and, finally, collapse or shock with pallor, clammy, cold

skin, dilated pupils and respiratory excitement and, later, failure.

To my mind it is quite proper to consider a possible adrenal cause for each symptom just enumerated. Very often it may be the chief cause and, too, other causes which also may be present are in part due to the adrenal factor.

Perhaps we might recapitulate just what Cannon demonstrated. He showed that the emotion of fear suffices to cause an increased stimulation of the flow of the adrenal secretion, and blood taken from the adrenal veins of frightened animals is so rich in adrenin as to be able to inhibit the peristaltic contraction of isolated strips of intestinal muscle which were immersed in the blood. This also has been shown to result from the presence, in appreciable amount, of adrenalin since contact with this commercial chemical substance in a dilution as insignificant as 1:1,000,000 will bring about the same experimental results upon isolated intestine.

Some day a comparatively easy technic will be evolved for the clinical measurement of adrenal activity. Many a time I have wished that I might be able to determine the degree of adrenal functioning in a given case. For example, some individuals are more susceptible to external impressions than others, and of these there are some who suffer much longer as a result of serious excitement than others; they "take a long time to get over" such experiences. If, now, we were able to estimate

with some degree of comparison the adrenin content of the blood of these persons, we would be able to know whether the adrenal element was prominent, could measure the degree of its depletion or excitation, and, naturally, would be better able to control the deviations from the average.

On the other hand, in cases suffering from the after effects of this excessive stimulation, as in shock, collapse or severe asthenia, we might be able to estimate in actual figures the factor of restoration and see how well and how rapidly the depleted adrenals were unable to functionate. In other words, we would be able to measure hyper- or hypo-adrenia.

A means of accomplishing this has been suggested by Ehrmann, and is sometimes called "the frog's eye test." It consists of immersing a recently enucleated frog's eye into the blood serum of the patient under examination. One notes the time elapsing from the moment that the eye is immersed in the serum, until the pupil reaches maximum dilatation. This may be compared with a scale previously made by performing the same experiment with definite solutions of adrenalin. It is thus possible to estimate comparatively the amount of adrenin present in the blood serum examined, though this method is somewhat crude and by no means accurate, for we do not know with certainty that the mydriasis is of purely hormonal origin. Also adrenin and adrenalin are very easily oxidiz-

able substances, and this militates against an altogether dependable test. There is no doubt, however, that some day we will have a clinical diagnostic procedure for the determination of the extent of the adrenal activities. I have suggested that some sort of a colorimetric test should be possible, and before long I believe that some chemist or physician is going to work it out.

The interrelation of the endocrine glands is so complex and intimate that it is practically impossible to have a marked deviation from the functional normal of one gland without a corresponding increase or decrease in the work of the others. This is the basis of the complexities of endocrinology and the reason for the numerous reports of pluriglandular disorder we are beginning to find in the literature. Parenthetically, it is often also the reason for failures in the treatment of this class of cases, for a presumed thyroid disorder is treated as a thyroid disorder pure and simple, when further investigation would couple one or more glands with it—often the pituitary, gonads or adrenals—and the treatment modified by this broader view would be much more effectual.

So adrenal stimulation by emotional causes, by toxemia or by changes in the hormone balance, may cause other ductless glandular disorders. For instance, fright often has much to do with the onset of hyperthyroidism. I have seen a severe shock cause exophthalmic goiter over night. Crotti

mentions the case of a man of 42 who had Graves' disease which developed in a few hours at the time of the San Francisco earthquake. I commonly find indications of this relationship in my consultation work, and there are numerous reports in the literature to substantiate this. In such cases I am convinced that the etiologic influence is not so much nervous as hormonic; and I explain this to myself by presuming that the undue stimulation of the adrenals by emotional strain causes a severe increase in their secretory activities which, so to speak, gives a very strong push to the thyroid pendulum, causing it to swing much more rapidly and in a longer arc.

While we are speaking of hyperthyroidism, I would like to remark that anger, fear and, especially, worry are factors which play a very important part in the treatment of all forms of this disorder. I have a case at present in whom the symptoms are always aggravated by concern over home matters, and the best of treatment, with absolute rest in hospital or out, is largely overbalanced by the fears and worries so difficult to control. A part of the proper treatment of hyperthyroidism is not merely rest, but absolute quiet away from the "hospital noises" and the removal of all things likely to disturb the emotional balance; in other words the prevention of adrenal stimulation just as Crile prevents this same thing in his surgical work by his methods of pan-anesthesia. The

administration of adrenalin, or the equally useful adrenal substance, may in some cases offset severe adrenal depletion.

Undoubtedly adrenal dysfunction is capable of causing digestive disorders. Crile has shown experimentally that among the functions of the adrenals is the power to inhibit intestinal function provided the adrenals are working to excess. Cannon confirms this, and has proved that a forced output of adrenin produces an increase in the arterial tension by shifting the blood from the comparatively less important abdominal viscera to the immediately essential organs as the brain, lungs and heart. It seems that there is enough clinical proof to implicate the adrenals in epilepsy. Adrenal excess tends to increase circulatory stasis in the brain, inhibits both pancreatic digestion and intestinal muscular activity and thus favors toxemia; factors which unquestionably are prominent in the syndrome of epilepsy. We all know that fright may be a part of the original cause of epilepsy, and also that a sudden shock or grief may badly upset the digestion.

Some interesting comments on the relation of the adrenals to intestinal stasis and epilepsy are to be found in a recent paper coming from the New Jersey State Hospital. Cotton and his associates there conclude that at least one type of epilepsy is probably a disease process dependent upon the absorption of toxic products from the intestinal canal.

This stasis may be produced by an overaction of the adrenal glands which, in turn, may be caused by dysfunction of the pituitary body or the pancreas, irritation of the duodenum, or severe fright or emotional disturbance. They then suggest that the administration of pancreatin should be employed in preference to surgical measures in the treatment of epilepsy. Incidentally this form of organotherapy is physiologically opposed to the action of the adrenals; it favors digestion, and it has been remarked that the pituitary is also an antagonist of the pancreas. At least Cotton's 25 or 30 cases encouraged him to make the above deductions and to report his good results with pancreatic organotherapy in epilepsy. I mention this for what it is worth; at least it amplifies my opinion regarding the importance of the adrenals in this disease. Note especially that toxemia causes hyperadrenia; that hyperadrenia causes toxemia (a vicious circle) and intestinal insufficiency, factors involved in many another syndrome besides epilepsy.

Pottenger has been doing some very interesting work involving the adrenal glands with some of the findings in certain forms of pulmonary tuberculosis. He has shown quite recently that the continued stimulation of the adrenals, presumably by the toxins of this disease, and the continued pouring into the blood of even minutely increased amounts of adrenin, brings about conditions resulting from sympathetic stimulation, including

the very dry mouth not uncommonly seen in tuberculosis, as well as other clinical findings, as the rapid heart action and the sudden and quite serious disturbances of digestion that one meets from time to time in tuberculosis.

I have put forward a theory regarding the adrenals in malaria which is yet to be discredited or proved. I believe that at one stage in the cycle of experiences in malaria there is a decided adrenal excitation, due to the sudden periodical liberation of the plasmodia and, of course, their toxins. One encounters the dry mouth as often as salivation, both manifestations of sympathetic stimulation. The heart action is always rapid and sometimes irregular. Then, as an aftermath of the chill, we find the muscular relaxation, prostration, depression and asthenia, all of which are identical with the findings of severe adrenal insufficiency.

If this idea is reasonable it should apply with equal force in other toxic infectious diseases and acute toxemias, such as typhoid fever and pneumonia; and Josue, Sergent and other French writers have accumulated undeniable evidence to show that the ultimate outcome of acute infectious disease includes a very severe adrenal depletion which not uncommonly may be the actual cause of death.

The most frequent form of serious adrenal disorder, then, is not Addison's disease, but what Sajous has called "terminal hypoadrenia." This is the frequently fatal ending of septicemia and all

serious toxemias as diphtheria, cholera and the like. In fact the algid stage of cholera, like the fatal "turn for the worse" in erysipelas or pneumonia, is brought on when the severe bacterial poisoning and accompanying cellular depletion causes acute hypoadrenia with collapse, heart weakness, a drop in the temperature and death. In such desperate stages the tide has been turned by intravenous injections of adrenalin, as much as 30 min. of the 1:1000 solution having been given with a happy outcome. This fundamental principle is worth remembering in such extremes, for the logical treatment is occasionally amazingly resurreктив.

In gynecological practice the adrenal glands may play an important role. I shall shortly direct your attention to their relationship to neurasthenia, and here wish you to recall the frequency with which severe asthenia accompanies ovarian disease. To illustrate, I recently saw a case in Omaha of extreme asthenia. This came on periodically in connection with the menses, and during the month there were, perhaps, five or six days in which the extreme lassitude and inability to accomplish anything were slightly modified. The weakness was absolute and had continued for years. The diagnosis was hypoadrenia superinduced by dysovarian or ovarian toxemia. In this case surgery gave some benefit, I believe, for a diseased ovary was removed in my presence and a cyst in the other was also removed. From the standpoint of this

paper the case was of special interest, for the myasthenia as well as the neurasthenia was undoubtedly due to the abnormal stimulation of the chromaffin cells by this poisonous ovarian hormone, and the patient was thus in a practically perpetual state of hypoadrenia.

I do not wish to commit myself to-night, but I have studied a number of cases of functional dysmenorrhea from the standpoint of endocrinology, and I must confess that I have strong suspicions that many of the symptoms, especially those of a sympathetic nature, are of adrenal origin; and if so the trouble is probably brought about by this reflex (hormonic) stimulation of the adrenals by the ovaries.

There is much reason to believe that adrenal dysfunction is a factor which deserves a good deal more responsibility placed upon it for the causation of neurasthenia than as yet has been given to it. In a recent article in my series, "The Diagnosis of the Internal Secretory Disorders" (Western Medical Times, Sept., 1916) you will find an outline of some facts connecting the adrenals with neurasthenia. I will quote a few paragraphs here:

"Minor functional hypoadrenia is more common than some have appreciated, and the fact that there is a psychic origin as well as other physiologic causes already considered, allies it to the fashionable 'neurasthenia' of to-day. In fact some have stated that what is improperly called 'neurasthenia'

is not a disease *per se*, but really a symptom complex of ductless glandular origin, and that the adrenals are probably the most important factors in its causation. Campbell Smith, O. T. Osborne, Tom Williams and others, including the writer, have directed the attention of the profession to the importance of the adrenal origin of neurasthenia (though a pluriglandular dyscrasia is practically always discoverable), but so far this is not understood as well as its frequency and importance warrant.

"The subject is too large to receive exhaustive consideration here, but a few quotations from recent literature will firmly establish the importance of this angle from which to study this common and annoying symptom complex. Quoting first from the Journal of the American Medical Association (Dec. 18, 1915, p. 2166): 'The typical neurotic generally has, if not always, disturbance of the thyroid gland. The typical neurasthenic probably generally has disturbance of the suprarenal glands on the side of insufficiency. The blood pressure in these neurasthenic patients is almost always low for the individuals, and their circulation is poor. A vasomotor paralysis, often present, allows chillings, flushings, cold or burning hands and feet, drowsiness when the patient is up, wakefulness on lying down and hence insomnia. There may be more or less tingling or numbness of the extremities.'

"Again Kinnie Wilson, of London, in his monograph on 'The Clinical Importance of the Sympathetic Nervous System' makes the following pertinent remarks: 'Many of the common symptoms of neurasthenia and hysteria are patently of sympathetic origin. Who of us has not seen the typical irregular blotches appear on the skin of the neck and face as the neurasthenic subject "works himself up into a state"? The clammy hand, flushed or pallid features, dilated pupils, the innumerable paresthesias, the unwonted sensations in head or body, are surely of sympathetic parentage. In not a few cases of neurasthenia symptoms of this class are the chief or only manifestations of the disease. Here, then, is a condition of defective sympathetico-tonus; may it not have much to do with impairment of function of the chromophil system? . . . There does not appear to be any tenable distinction between the asthenia of Addison's disease and the asthenia of neurasthenia. Cases of the former are not infrequently diagnosed as ordinary neurasthenia at first. It is difficult to avoid the conclusion that defect of glandular function is responsible for much of the clinical picture of neurasthenia.' "

Be prepared to look for the adrenal element in gynecology or in neurasthenia and it will surprise you how common it really is. Kinnie Wilson, in the same address from which the above quotation was made, also made the following apothegm:

"Sympathetic tone is dependent on adrenal support, and until the glandular equilibrium is once more attained, sympathetic symptoms are likely to occur."

In closing I might point out that these reactions resulting from adrenal excess possibly may explain the occasional effects of psychanalysis, suggestion and even Christian Science in certain neurotic or, more properly, sympathetico-tonic states. One can readily see that a calmed mind—reduced emotional overstrain—obviates the excessive psychic stimulation of the adrenals; and the hypertonic state of hyperadrenia or the later asthenic state of hypo-adrenia are thereby allowed to right themselves by Nature.

This may be visionary, but I still insist that we are going to connect the adrenal glands with numerous conditions encountered in general practice, particularly those connected with the emotions, more and more as we come to understand their functions and interrelations better.

## VIII

### THE ASTHENIAS: NEURASTHENIA, PSYCHASTHENIA, MY- ASTHENIA AND CHEMASTHENIA— ENDOCRINASTHENIA

OF ALL the difficulties encountered in general practice the asthenias constitute quite a large percentage. Naturally neurasthenia occupies a prominent place, but this is by no means the only asthenia which we have to meet. It is the opinion of the writer that endocrinasthenia is a very much more important condition than yet appears. In fact this word is not yet found in our most recent dictionaries and while there is plenty of literature upon ductless glandular insufficiencies, so far as I know the subject has not been extensively considered from this angle.

The hormones, or the “regulators of metabolism” as Noel Paton has called them, bring about a series of chemical reactions which really must be considered as sthenic in character. The word “hormone” comes from the Greek, “I arouse,” and it is not a very great stretch of imagination to consider asthenia as representing “I lie down.”

There is an accumulating weight of evidence in clinical practice which is being reflected in current literature which indicates that many forms of asthenia properly may be called of endocrine origin

or endocrinasthenia. The arousing stimuli are lessened or lost. The body, or a part of it as the case may be, is tired out, function has been disorganized by numerous factors and the resulting loss of strength and activity may affect the muscles, nerves, mentality, metabolism or, for that matter, any other bodily function. It seems quite reasonable to believe that if the endocrine glands are affected by conditions which render them inactive, the natural outcome would be a condition of general functional somnolence, or as we call it "asthenia"; while any attempt to bring about greater activity on the part of the glands of internal secretion must necessarily arouse the metabolic functions in general as well as certain of the results of this hormonic function in particular.

If this is the case, we must revise our consideration of the origin as well as the treatment of all forms of asthenia and from a practical standpoint this seems to be a profitable advance in medicine, for when we treat the various asthenias with the internal secretory factor prominently in our minds, the results really seem to be better and more permanent than though we merely prescribe rest and a hygienic regimen calculated to reduce the toxemia.

Of course rest is most advantageous in the treatment of all forms of fatigue whether natural or pathologic, though many individuals suffer from forms of tiredness which are not remedied by in-

activity and sleep—they are the ones who “get up tired.” Preventive measures usually do not suffice to secure tangible results in cases of this character, and treatment calculated to remove as many of the obvious conditions favoring the asthenia is very much more satisfactory in its results if efforts are made simultaneously to re-establish the normal hormone producing functions.

With these preliminary considerations in mind we will consider briefly the various asthenic states and attempt to connect them with one or more of the glands of internal secretion and, having done so, it must be left to the reader to apply his own deductions and modify his treatment of asthenic states accordingly.

To those who take time to study endocrinology in its relation to the practical side of medicine, it becomes quickly apparent that the most important functions of the glands of internal secretion are of an aggressive or stimulating nature, and further, that the most common endocrine disorders are in the nature of an insufficiency. With all such insufficiencies, whether they be thyroid, pituitary, adrenal or gonad in origin, asthenia is an almost invariable accompaniment. The chief diagnostic or clinical necessity then, would appear to be the appreciation of early forms of endocrine insufficiency or hypocrinism and, where possible, the differentiation or evaluation of functional insufficiency of the glands that are affected.

The thyroid gland is responsible for a very large measure of the metabolic activities of the body and is susceptible to the subtle influences of numerous very common disorders, for toxemia of all kinds affects the thyroid as early as any other part of the body and infections, whether general or focal, not infrequently disturb the normal functioning of this gland. The French have called the thyroid "the emotional gland" since it is intimately related to the emotions, but we now believe that much of this supposed connection is not direct, but is brought about through the intimacy of the adrenals with the thyroid. Theoretically these conditions should stimulate the thyroid and it is perfectly true that many cases of thyroid excess are the result of just such stimuli, but it is none the less a clinical fact that insufficiencies are more frequent than the opposite conditions and hypothyroidism, especially the minor form, is very much more common than hyperthyroidism.

The clinical importance of the minor forms of thyroid insufficiency has been fully discussed elsewhere\* and if the study of individuals suffering from any form of asthenia is made to include a search for definite indications which would lead one to incriminate the thyroid gland, treatment calculated to stimulate this gland is very likely to make a favorable impression upon the course of the

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\*See Chapter IV.

disorder.<sup>†</sup> If one reads much of the literature on thyroid disorders and even limits it to the writings of Eugene Hertoghe, Leopold Levi, George Murray or Gabriel Gauthier he will be quickly convinced of the extreme frequency of asthenia as a manifestation of all forms of subthyroidism from the most insignificant and easily overlooked to the best clinically defined or text-book varieties.

Our knowledge of the adrenal glands is inextricably connected with asthenia for the most prominent of all the symptoms described in 1855 by Addison, is asthenia of a most marked type. Of course Addison's disease is an organic adrenal disorder and it is not necessary for an individual to be suffering from this incurable disorder in order to have the symptoms of functional adrenal insufficiency. As a matter of fact this latter disorder is almost as common as the minor functional thyroid troubles to which attention has just been drawn, and as we now believe that the adrenals are depleted as a result of the stimuli of emotion, toxemia, pain or certain disorders of other glands of internal secretion, we can readily see how easy it is to incriminate these glands in the asthenias as a class. The clinical findings in severe hypoadrenia, quite different from the Addison syndrome, always include asthenia as a most prominent condition, for what is shock or collapse if it is not an extreme

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\*This treatment, by the way, may be numbered among the few "specifics" which we have in medicine.

manifestation of vasomotor as well as muscular asthenia?

The pituitary gland, too, exerts what properly might be called a sthenic effect. Its influence alone is not quite so marked as that of the adrenals or the thyroid, but we know that the posterior lobe at least contains markedly stimulating substances and it should not be improper to presume that deficiencies in the production of this and other similar substances in either lobe of the gland must exert some opposite effect upon the organism. In fact recent German writers have definitely connected certain forms of cachexia with pituitary insufficiency and seemingly have established their contention by modifying these conditions with pituitary feeding.

We also know that pituitary insufficiency is sometimes responsible for a syndrome described by Froehlich and Bartels in which metabolic insufficiency (chemasthenia) is present as well as a deficiency in the production of the so-called dynamogenic hormones with a resulting infantilism or asexuality. I recall a very interesting case of asexuality unaccompanied by any findings which would warrant the diagnosis of the Froehlich syndrome, in which a radiographic examination of the sella turcica showed a very decided diminution in size of the pituitary body. Additional evidence from the opposite side is now discoverable in the literature and I have had some favorable clinical experi-

ences myself with the administration of pituitary substance in functional impotence.

Tom Williams of Washington, in a most interesting discussion of the endocrine neurasthenias (Medical Record, April 14, 1917), tells of an obscure condition in a business man which was described as "a general feeling of discomfort, sometimes with intense fatigue" which was traced eventually to a disorder of the pituitary gland.

Without a doubt the pituitary must be considered as a possible factor in the production of many of the asthenic manifestations and while the Abderhalden test as amplified and made practical in the Corson-White laboratory in Philadelphia, is often helpful, it is not so difficult to secure a sellar radiograph in suspected cases.

The thymus gland is perhaps the least appreciated and understood of the glands of internal secretion. Its persistence in the adult is often accompanied by a severe asthenia, especially myasthenia, and thanks to the work and writings of G. H. Hoxie of Kansas City, we are beginning to understand more about this clinical relationship. It should not be amiss in the study of a well defined asthenia which resists treatment, to establish or rule out by careful physical diagnostic measures and the X-ray the possible presence of a persistent thymus.

Still another gland recently has been associated with myasthenia. Timme (Archives of Internal

Medicine, Jan., 1917) has intimated that that intractable neuro-trophic disease, myasthenia gravis, may be quite likely of endocrine origin and the epiphysis or pineal gland a possible source of its cause. This has not been proven, but it may be that once again an enigma heretofore unsolved will be made clear by a broader knowledge of endocrinology.

The sex glands are unquestionably the drivers of the organism. It is not necessary to dilate upon the relation of their activities to muscular, mental or metabolic function. There is much clinical evidence to establish this position and the renowned experience of Brown-Sequard who injected testicle juice into himself and discovered an immediate enhancement of his physical powers and endurance as well as a diminution in the asthenia due to his age, was really the beginning of scientific organotherapy, and times without number since 1889 the hormonic importance of the gonads has been established experimentally and clinically, as well as therapeutically.

The natural corollary of the discovery of a glandular insufficiency is an attempt to re-establish it, and the most satisfactory and scientific manner to accomplish this is by recourse to judicious organotherapy. It is true that these insufficiencies rarely are seen singly and that ductless glandular disorders invariably affect several or all of these organs, hence while this complicates our diagnostics

and favors a tendency to empiricism, none the less we cannot permit ourselves to ignore endocrine deficiencies just because we may not be able to label them accurately or to measure the comparative deficiencies of this gland or that. Without a doubt the "unscientific" administration of mixed glandular extracts whether proprietary as "hormotone" or otherwise (as, for example, the "Tabloid mixed glands" suggested by E. B. McCready of Pittsburgh) has remedied materially many hundreds of cases, and it is my custom when attempting to treat an asthenia, whether neurasthenia, myasthenia, psychasthenia or chemasthenia, to consider it always as a manifestation of endocrinasthenia and to supplement the hygienic and other allied measures with the indicated glandular feeding or, in suitable cases, with the hypodermic administration of the so-called Roberts-Hawley lymph combination of which, unfortunately, there is still too little said in current medical literature.

## IX

### THE RELATION OF THE INTERNAL SECRECTIONS TO NEURASTHENIA IN WOMEN

"THE condition called 'neurasthenia'—a symptom-complex rather than a distinct disease—is being more carefully studied these days. Our knowledge, however, still seems to be just as indefinite to-day as it has always appeared to be, for the opinions regarding neurasthenia have differed even more than the ideas of all medical men usually differ. It would appear that the organs of internal secretion are to be charged with causing many of the disorders which together form the neurasthenic syndrome. In fact the more we study the neurasthenic individual and observe closely the incidental variations in functional activity, the more evident it becomes that neurasthenia rarely exists without some associated disturbance in the work of the ductless glands."

The foregoing quotation from an editorial in American Medicine (August, 1915, p. 590) is a fit introduction to the subject that has been chosen for consideration this evening. As our knowledge of these glands of internal secretion becomes more extensive and connected, one can appreciate more

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An address read before the Los Angeles Obstetrical Society, December 14, 1915, and reprinted from the American Journal of Obstetrics and Diseases of Women and Children, April, 1916.

thoroughly how intimate is their association with one another, as well as with the etiology of many functional disorders and even, occasionally, an organic disease. In no phase of endocrinology do we see that intricacy of these relationships more definitely, than in the numerous functional disorders, the treatment of which constitutes the largest part of the work of the gynecologist.

From the time that the thymus begins to retrograde and its antagonism to the functional activity of the gonads is gradually reduced, there is an increase in the physiologic activities of the thyroid and the ovaries, as well as in most of the other ductless glands which are built in with these keystones of the endocrine arch. It is an everyday occurrence to see thyroid enlargement at puberty, and it is now well known that the essential sex manifestations as well as the organic changes which accompany them, are due to the production of a series of chemical messengers and the maintenance between them in the fluids of the body of what has come to be known as the "hormone balance."

Disturbances of this balance are responsible for most of the functional disorders in women. This is a broad statement, I know, and it will be questioned by some who still are certain that the nervous system and derangements of it, are responsible for many functional gynecological disturbances. However, it has been stated by more than one in-

vestigator of authority that the nervous system itself, and more especially the sympathetic nervous system, is under the direct control of certain of the endocrine organs; and the conclusions made by Cannon, of Harvard, as to the relation of the emotions to adrenal activity, indicate that the adrenal medulla is a prominent factor in the causation of many manifestations commonly associated with fear, rage or pain. Now the chromaffin tissue of the adrenal medulla is but an integral part of the endocrine system, and is just as intimately connected with the other parts of this system as are the thyroid, pituitary, ovaries or any other of the ductless glands; hence if disorders which are dependent upon emotional disturbances really have an internal secretory basis, it is obvious that very few functional troubles in women are not in that category of disturbances now being differentiated and called "endocrine disorders." Practically all such conditions are in a greater or less degree amenable to organotherapy procedures, and the more these are applied in clinical practice, the more are we convinced of the importance and extent of this comparatively new class of disorders.

It is difficult intelligently to discuss a subject as broad as neurasthenia. First of all it is not really an entity, but rather a symptom-complex with varying manifestations. While it is found in both sexes, it is much more common in women, and most frequently is connected in some way with one or

more disorders of the sex apparatus. When a patient comes to us with a combination of symptoms which the clinical history seems to connect with a menstrual disorder, deranged or misused reproductive functions, climacteric irregularities or a general run-down condition, if there is a nervous element in the case—and in how few is there not? —it is very easy to call it neurasthenia.

As a matter of fact it is impossible not to have neurasthenia in patients who are below par, for when an individual is asthenic and debilitated, the nervous mechanism is likely to be just as asthenic as the muscular system, the eliminative system or the endocrine system; and when we meet women who are hysterical or melancholic; excitable or apathetic; menstrually plus or minus (if I may use such a term); or are suffering in some way as a result of an over- or under-activity of the genital organism, we might better consider them from the standpoint of the internal secretions rather than to classify them as neurasthenics and give them tonic or sedative treatment according to the exigencies of each case.

I have come to the conclusion that it is not possible to treat functional gynecological disorders effectively without in every case carefully considering each individual from this standpoint. The ductless glandular system in women is as sensitive to physiologic impressions as the nervous system; hence one must expect to encounter pluriglandular

disturbances very frequently.<sup>1</sup> The principal reason that this does not seem to have been done more often is because the subject has not yet reached that stage of stability which some physicians insist upon. You know that there are still members of our profession who deny the "hormone theory," as they like to call it; and with this, of course, they virtually deny the feasibility as well as the applicability of organotherapy. It is to be hoped that everyone present this evening is safely out of this class, and that all will admit with me the probable relationship of ductless glandular disorder with the majority of those cases usually called "neurasthenics." If so, a few suggestions of a therapeutic nature may be acceptable, and the discussion which follows doubtless will bring out considerably more of practical value than does this paper.

There is a comparatively small number of women whose neurasthenic manifestations are associated with ovarian and menstrual superactivity. Their periods are prolonged and excessive, they have so little freedom from the inconveniences of menstruation and their economy is so depleted by the undue loss of blood and strength, that they easily become neurasthenic. Often they brood over their condition; and, rarely, the onset of a heavy flow prostrates them not merely physically but mentally. All too often these cases are called "endometritis" for convenience and are treated surgically with mediocre results; while many might be benefited by the

exhibition of mammary extract. This substance antagonizes ovarian activity, depletes the uterine vessels and is an excellent means of controlling functional uterine hemorrhage. Incidentally it has been given with good results in uterine fibroids, not only stopping the hemorrhage but, in an encouraging proportion of cases, reducing the size and stopping the growth of the tumor. But this is taking us from the subject of the evening. Mammary extract is given in 5-grain doses, preferably at meals. Ten grains three times a day is usually the maximum and if this is continued for two or three weeks, then omitted during the days free from menstrual flow and started again, and if necessary pushed, during the flow, to be discontinued again till the next menses and given in this manner for two or three months, the effects of the increased ovarian activity will be reduced and the benefit will usually embrace other symptoms than the one for which mammary therapy originally was instituted.

A larger number of neurasthenic women exhibit the opposite pelvic conditions, and suffer from delayed or insufficient menses. This is but one symptom in a chain of disorders due to hypoendocrinism (hypocrinism)—reduced internal secretory activity and one which gives us an excellent opportunity to apply the principles of organotherapy, and not only remove the menstrual disabilities but with them the associated neurasthenia. Such individuals are usually anemic, insufficiently nourished and toxic.

They are flabby, often obese and do not react well to the morning bath (which, by the way, very few of them take) or to treatment of any kind. Their cells are physiologically lazy and asthenic (although they may be mentally bright and despite their troubles may attempt to be quite active physically). Yet always associated with these common conditions there is a more or less marked nervous element which is usually singled out and given undue prominence in the nomenclature as well as the therapeutics, for, of course, such cases are obviously "typical cases of neurasthenia."

The cellular inactivity of such individuals almost invariably indicates a condition of minor hypothyroidism, in fact this disorder may be the principal basic cause of the whole trouble, for it is surprising how many times the thyroid may be responsible for functional disorders of many kinds. (By the way, this statement is not made thoughtlessly; for many functional cellular disabilities can either be traced to hypothyroidism or shortly after the onset are aggravated by an associated thyroid inadequacy; and while in some cases other factors may be predominant, to the seeing eye there is usually a path of more or less prominence which leads to the thyroid mechanism). This hypothyroidism, in turn, may cause a reduced luteal activity and when it is sufficiently marked to be clinically evident, many of the endocrine glands are already working at half speed or even slower. This explains the good results fre-

quently obtained from pluriglandular therapy in such cases, of which more shortly.

This action is strictly speaking a reflex action, and the use of this term needs a brief qualification. It may be and probably is nervous, but it is also and more decidedly hormonic in origin. The thyroid produces an internal secretion which stimulates the ovaries and their corpora lutea, hence a "reflex" influence of reduced thyroid action is a correspondingly reduced luteal action, and so on. This means that there may be cases of amenorrhea of distinct thyroid origin; and it is of interest to recall that Prof. Dalche, of Paris, regards amenorrhea and especially dysmenorrhea in young women, as definitely due to thyroid rather than ovarian disorder. He reports the successful treatment of many cases of this character by giving thyroid alone, the dose usually being 1 or 2 centigrams per day in divided amounts.

By far the greatest number of menstrual neurasthenics, as well as practically all sexual neurasthenias in women, have their origin in a functional derangement of the internal secretory portion of the ovaries. This, of course, is the corpus luteum, although the ovarian stroma has been shown to exert a certain but minor influence of this nature. Since the development of a corpus luteum is supposed to be synchronous with the onset of menstruation, per contra, the absence or semi-absence of the menses is often due to a decreased production

of the luteal hormone. This disturbs the delicate hormone balance, already referred to, and is directly concerned in bringing about certain neurasthenic manifestations, at the same time reflexly (hormonically) producing a vicious circle.

The whole subject is being studied experimentally in several laboratories and many hundreds of clinical applications are being made from week to week, although but a small number of them are reported for the benefit of the profession. It may be said unequivocally that there is an incontestible relation between the physiologic action of the corpora lutea and neurasthenia. Howard Kelly and C. H. Burnham of Baltimore have established this on a practical basis and have reported a number of cases of typical neurasthenia in women, which were successfully treated with lutein. R. T. Frank of New York, Adam Leighton of Portland, Me., Paul Carnot of Paris, W. Blair Bell\* of Liverpool and several others that I might mention, have expressed themselves on this subject, and we cannot but conclude that not only is neurasthenia frequently due to functional disturbances in the hormone production of the ovaries, but that it may also respond favorably to suitable doses of luteal preparations.

In passing it may be well to mention briefly a

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\*I feel it a privilege to add here that my friend Dr. Blair Bell recently has published a book entitled "The Sex Complex" (Bailliere, Tindall & Cox., London, or Wm. Wood & Co., New York), in which the relation of the internal secretions to the female economy is taken up in a masterly and interesting fashion.

form of neurasthenia accompanied by dysmenorrhœa in women near the menopause. These cases are usually obese and metabolism is invariably reduced. Lemaire of Paris believes that most cases of this character are due to a disturbed equilibrium between the internal secretory glands, and he recommends in such cases the administration of combinations of thyroid and luteal substances. In his experience he finds that this treatment not only reduces the pain and discomfort at the menses, but also enhances the metabolism and many times controls the distressing neurasthenic manifestations.

Another of the ductless glands likely is concerned in many cases of neurasthenia in women. The pituitary body and its various distinct parts are not so well understood as the thyroid or the corpus luteum; but the hypophysis is none the less a part of the endocrine system and as such exerts some influence upon such a broadly extending complexity as neurasthenia. Neurasthenia is not infrequently a side-issue in cases of dyspituitarism and as we have opportunity to study more closely these relations in women with pituitary disease, we will be able to speak with more authority on this phase of the subject. From a practical standpoint we do know, however, that the administration of total pituitary substance has a beneficial and quite general tonic influence, especially in those indefinite, asthenic cases where the nervous and muscular efficiency seems to be especially deficient. As

an empirical remedy in such cases, as well as in certain pluriglandular insufficiencies, pituitary substance (whole gland) is helpful because of its tonic action upon cardiac, intestinal and uterine muscles; and while there still may be only slight scientific ground for giving it in many cases, it is of undoubted clinical value, and when an eminent man like Leonard Williams, of London, expresses his faith in pituitary as a remedy for amenorrhea and menstrual neurasthenias, I am content to believe without the "incontestible scientific proof" that some physicians still insist upon—in public! Incidentally I would like to ask how it is possible to establish a subject relating to therapeutics upon this hypothetical plane of indubitability without a certain amount of clinical experience; and if we are to refrain from empiricism, how are we to progress?

This same Leonard Williams has also found pituitary of value in those cases he amusingly calls "the moth-eaten old ladies who come out of boarding houses to go to church"; and it will also be found useful in the elderly, inactive, neurasthenic women who, perhaps, are not always found in this same rare category. In a paper read before the Royal Society of Medicine, which I had the pleasure of hearing some years ago, Williams spoke favorably of a pluriglandular preparation called hormotone, which is a combination of the three glands mentioned this evening—thyroid, pituitary and ovaries. In my own limited experience I have found

this frequently superior to corpus luteum alone (save only in cases where the ovaries have been removed and cannot therefore respond to the homostimulant action of the luteal ingredient); and it has the advantage of costing considerably less, for unfortunately corpus luteum is still an expensive remedy and the recent increased demand seems to be making the price go up, rather than down, as one might presume. At all events I have seen good results from this combination in neurasthenia in women.

In cases with amenorrhea the increased action of the thyroid and ovaries not uncommonly has re-established the flow and associated nervous manifestations due solely to the repression of this function, were also controlled. In the nervous manifestations of the artificial menopause, especially in comparatively young women, it is not so effective unless corpus luteum is given with it, in the proportion of 5 grains of corpus luteum to one or two tablets of hormotone, three times a day. In dysmenorrhea occasionally it has stopped the pain almost like a sedative drug, while again in seemingly identical cases it has seemed to be quite inert. (Parenthetically this is not an uncommon experience in organotherapy practice.) One cannot always depend upon similar results from the same treatment in presumably similar cases. The influence of these hormone-bearing preparations is rarely directly due to the action of the principles they con-

tain, but rather to the results of their homostimulant action; i. e., to the increased activity of the glands which they stimulate and the enhanced hormone production. Perhaps an explanation of this somewhat discouraging experience lies in lack of persistence, for not always are the ductless glands as easily stimulated, while in some of the rapid-acting cases the startling results are brought about because the missing but all essential touch is given to the pendulum, and it starts again.

In the nervous and circulatory disturbances of the menopause pluriglandular therapy is worth trying, for these symptoms are in most cases naught save the natural results of the removal of stimuli to which the body has accustomed itself for thirty years or more.

There are other phases of this subject which will occur to you. In some cases the endocrine element will be very apparent when one is looking for it; while in others it is not easy to demonstrate. In such cases, however, it is there none the less and I prefer to imagine that this unnoticed factor is playing some minor role, and that the more obvious manifestations of diagnostic value have not yet become sufficiently marked to be differentiated.

In conclusion, the administration of thyroid, corpus luteum or pituitary gland, or combinations of them, to my mind is as rational a form of the treatment of many of the functional neuroses in women, including neurasthenia, as one could hope for. Of

course, such remedies do not militate against the hygienic procedures or even drugs that may seem to be indicated, on the contrary one will often find that organotherapy renders the response to other treatment much more satisfactory.

In applying the principles of endocrinology in the consideration and treatment of neurasthenia in women, we are removing obstacles and assisting Nature; and where this is accomplished one can expect with much more confidence than otherwise, that Nature will be better able to bring about the much-to-be-desired outcome.

# X

## SEX DISABILITIES CONSIDERED AS ENDOCRINE DYSCRASIAS

EACH part of the endocrine system depends upon and influences each other part. Each of them is indispensable to the organism, though experimentally it has been shown that life is not necessarily terminated by the removal of one or more of these essential organs, though we know that the adrenal glands and the parathyroids are quite necessary to life.

Not least in importance among these “glands of life” are the gonads, and while their physiological importance to the economy as a whole is admitted, it sometimes seems that it is not appreciated, at least in therapeutics. There is no longer a question as to the internal secretory capacity of both ovaries and testes, nor can there be any doubt of the importance of their chemical messengers. Nevertheless it is a common thing to discover sex disabilities that have not been considered as endocrine dyscrasias, and more than often in consequence have been treated without success. The “bad name” given to the particular form of therapeutics inaugurated immediately following Brown-Sequard’s epoch-making announcement before the Paris Biological Society in June, 1889, was not deserved and, like the baneful effects of gossip, persisted long after its inherent value had been firmly established.

To the writer at least the method of treatment inaugurated by Brown-Sequard is rational because it is resultful. The personal experiences of this distinguished savant must be considered as well founded for the treatment was administered to himself in a scientific laboratory where the study of physiology was uppermost and under circumstances most favorable to calm and judicious consideration of the findings. And the experience of Brown-Sequard has been duplicated time and again for over thirty years.

Sex disabilities must needs be considered as resulting from internal secretory disorder because the sex manifestations are so absolutely under the regulation of the endocrine system. Not merely do the gonads bring about their subtle influences upon feature, form and function; but they themselves are played upon by the other ductless glands, and I do not think that there is a single endocrine disturbance affecting any of the glands of internal secretion that does not have in its syndrome some direct or indirect effect upon the gonads and their work.

The thyroid, best known of the glands of internal secretion, certainly exerts its influence upon the development and functional value of the ovaries or the testes, for the cretin is never sexually developed and the sufferer from myxedema acquires with the myxedematous characteristics typical changes in the sex manifestations which undoubtedly are due to the modified thyroid chemistry. The lack of the

thyroid hormone predicates gonad insufficiency.\* The opposite happens to be equally true, for hyperthyroidism is not uncommonly associated with hyperovarism, menstrual difficulties and, occasionally, erethism. Pelvic congestion is not an uncommon accompaniment of hyperthyroidism as every gynecologist well knows.

The pituitary gland is none the less intimately connected with the sex glands, and the best known forms of pituitary disease have as prominent clinical features, functional or even structural changes in the gonads. Hypopituitarism is sometimes called "dystrophia adiposo-genitalis" because the dystrophy makes itself so manifest in the genital form and function. Insufficiency of the pituitary gland spells genital insufficiency, while possibly pituitary excess may cause a temporary increased genital function, though this is not so common as in the opposite condition; and, too, it must be remembered that hyperpituitarism very commonly metamorphoses into hypopituitarism and this may account for the asexual manifestations occasionally seen in individuals with well defined changes due to an obvious pituitary excess.

The adrenal glands are also connected with the gonads, though there is not so much clinical data on this phase of endocrinology as in the study of the thyroid or pituitary glands. Nevertheless the

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\*And sex deficiencies should lead one to look for evidence of thyroid and other endocrine symptoms.

profession is now fairly unanimous that certain sexual complications have an adrenal origin, for instance the peculiar organic and functional changes called "virilism" in which the female characteristics are supplanted by obvious masculine characteristics, have been shown by Apert, Ballet, Tuffier and others to be the result of organic adrenal disorder. On the other hand Addison's disease is practically always accompanied by impotence. The functional form of adrenal insufficiency discussed in Chapter VII may be expected to be accompanied by some sort of sex depression, for the asthenia of hypoadrenia cannot well affect so many functions—circulation, muscular power, mental activity, etc.—without some influence upon the gonads. I have had several experiences which support this view and have had a number of illustrative cases brought to my attention. The case of ovarian poisoning referred to on page 86 is one. The case of shock following the "near accident" mentioned on page 74 is another. I heard of a physician who had been impotent for a year or more following an accident, whose hormone balance had been severely disorganized and whose blood pressure and other clinical evidences indicated a state of chronic hypoadrenia. Tonic hormone therapy restored this balance in a short time. In the chapter on shell shock (VI) I might have added that this condition is practically always associated with evidence of disturbances in the sex manifestations.

There is much evidence in favor of the suggestion that sex disabilities may be associated with or due to dyscrinism, and that the adrenal system, so-called, is intimately functionally related with the sex glands.

The relation of the thymus to the sex glands is now fairly well understood, and it has been shown that a persistent thymus is likely to be the cause of genital insufficiency, for the thymus itself produces a chemical antagonist to the gonads and as soon as it normally atrophies just before puberty, the sex glands are thus permitted to assert their chemical or hormonic functions.

Several of the clinical reports in comparatively recent literature indicate that parathyroid disease also exerts its influence upon the sex glands. While Parkinson's syndrome or paralysis agitans is not admitted by all to be a distinct parathyroid disorder, there is a good deal of evidence in favor of this position, and I have encountered not merely good results following the parathyroid method of treatment of this disease, but have seen the sex disability which is a part of the syndrome materially modified for the better following a longer or shorter course of parathyroid treatment.

At present the pineal is not supposed to be a gland of internal secretion although from my own standpoint it is difficult to explain many of the findings connected with epiphyseal tumors on any other basis than that of internal secretion. At all events

hyperpinealism has been shown to be accompanied by a very remarkable early ripening of the sex glands, and precocity both mentally and sexually. Whether this is of endocrine origin or not, it is a matter of considerable clinical interest.

With these briefly outlined facts in mind, we can not but conclude that the disabilities of sex always deserve consideration from an internal secretory standpoint. Dysgenitalism is dyscrinism, and clinically as well as therapeutically this position can be established beyond peradventure. Many a case of obscure neurasthenia will be found to be accompanied by a sexual neurosis which is really the bottom of the whole matter. Indeed, I am convinced that much of the success following pluriglandular therapy as outlined elsewhere,\* is largely due to a re-establishment of an unappreciated dysgenitalism. Many forms of organotherapy are known to affect genital function. Thyroid extract has been used time and again to control menstrual disorders. Its use has been equally efficacious in re-establishing a more nearly normal sexual development and activity in individuals suffering from both major and minor thyroid insufficiencies. The orthodox treatment of the Froehlich syndrome (*dystrophia adiposo-genitalis*) is pituitary feeding, and one of the therapeutic results is a favorable modification of sexual development and function. In fact pituitary feeding is beginning to be used with moder-

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\*See Chapters V, VI, VIII and IX.

ately good results in sexual insufficiencies not necessarily connected with well marked pituitary disease, and quite recently Stelwagen (N. Y. Med. Jour., 1917, ciii, 879) reports the successful treatment of a number of cases of functional impotence with 15 or more grains of anterior pituitary gland administered daily for a period. It is granted that this is a preliminary report, but at least it is a suggestive experience as we consider the particular subject under discussion.

Quite the most important phase of organotherapy in dysgenitalism is the use of extracts of organs corresponding to those affected—the ovaries or testes, as the case may be.

Corpus luteum has established itself as a standard remedy in many functional genital disturbances in gynecological practice, and its value is referred to elsewhere in this book; but somehow or another the corresponding treatment in the male still remains "under a cloud." The physician who would champion luteal preparations without a question, says little about the use of testicular preparations; and there is a very obvious question about this in the minds of the majority of the profession.

Despite this I have the utmost confidence in this phase of organotherapy. I believe that Brown-Sequard's findings were based upon good physiology and were not overstated, and while we will grant that there undoubtedly were many overstatements in the nineties, especially by the aggressive

quacks who seized upon Brown-Sequard's reports to fleece their gullible patients, this does not change the fundamental basis of reason for testicular organotherapy.

If functional impotence in the male as well as in the female is considered in the light of an endocrine dyscrasia, there is more hope of a successful outcome than from all the electrical, mechanical and psychotherapeutical procedures combined. The principle of homostimulation oft referred to in my writings applies just as much to the gonads as to the thyroid, pituitary or any other gland of internal secretion, and the clinical results following the use of Didymin, Sequarine, Hormotone, or the Roberts-Hawley Lymph, or any other preparation calculated to stimulate the sex glands to a greater functional activity, are based upon good physiology and sound reasoning, many statements to the contrary, notwithstanding. This is not the place for case reports. I have mentioned one or two previously and could extend the list materially.

Let us consider for a moment the philosophy of the last of these proprietaries. Unnumbered cases of so-called "incompetence" have been treated with this lymph. I have personally used it in my practice and am certain that this homostimulant action is the physiological explanation of the good results that one can expect to secure following its judicious use in cases of this character. I am equally convinced that the empirical administration of the

preparation Hormotone, or Tabloid Mixed Glands, in dysgenitalism is active through the augmented internal secretory activity of the gonads which thus may be brought about.

The beneficial effects from this kind of treatment seem to originate from the augmented gonad activity for this alone is sufficient to increase metabolism, to create force (the testicular hormone has been called "a dynamogenic hormone") and to start up a greater degree of functional activity in the other interrelated endocrine organs. This accounts for the unusual effects that have been reported following the use of the R-H Lymph in very chronic and much treated cases; as well as the more direct effects on impotence and hypogonadism.

I realize that statements such as the foregoing are open to criticism and that they will be criticised just as similar ones have been criticized for thirty years, but the opinions of critics count for naught as compared with the opinions of satisfied patients; and nothing can shake my belief that one is more likely to accomplish the desired therapeutic ends in the treatment of sexual disabilities if they are considered as endocrine dyscrasias and treated as such.

## XI

### THE RELATION OF THE INTERNAL SECRETIONS TO RHEUMATISM AND THE RHEUMATIC DIATHESIS

RHEUMATISM and the rheumatic diathesis are conditions concerning which the medical profession holds numerous and widely differing views. The literature regarding the various phases of rheumatism is as extended as it is contradictory. The unsuspecting reader frequently is led into a morass of differing conceptions from which it is not always the easiest thing to extricate himself.

Some writers insist that "rheumatism," and by that they usually include the varying disorders which have been classed under this name, is a manifestation of digestive trouble pure and simple; correct the digestion and the rheumatism will be automatically taken care of.

Others insist that it is essentially the result of an imperfect mineral metabolism and assure the reader that recourse to certain inorganic neutralizing remedies will quickly bring conviction regarding the correctness of this view.

Still others assert that there is a bacterial origin, not only for the obviously infective forms of rheumatism, but for all of them; and that the successful treatment of this disorder is not complete without

at least the addition of procedures based upon its "undoubted microbic origin."

Much has been written regarding the relation of uric acid to the rheumatic diathesis and opinions seem to be veering away from the statements so ably presented by Dr. Alexander Haig. In a recent communication (*Interstate Med. Jour.*, April, 1915) Goodman aptly remarks that: "The uric acid theory is at present tottering on its unstable foundations and we are growing more and more inclined to the view that not uric acid, but rather disturbances of intermediary purin metabolism, are at the root of the evil."

Looking at this problem from the standpoint of an average physician, it is altogether probable that there is an element of truth in all of the theories regarding rheumatism and that the statements which serve as a prelude to this article are all correct to a certain degree. None can deny that rheumatism in the majority of instances exhibits as one of its most constant manifestations a disturbance of metabolism, and considerable evidence is accruing to indicate that not a few of these cases have as the original basis of the trouble an obscure infective process which may never be so obvious as to direct attention to itself, but is only brought to light following the empiric use of stock vaccines given with the expectation that this unnoticed infection may be present. In such cases (and Sherman, of Detroit, has frequently directed attention

to the importance of this class) the diagnosis is often made by the clinical results of the empirical treatment and it may be stated in unqualified terms that many of the chronic rheumatic affections are of bacterial origin, even though they may show none of the typical findings of obviously infective cases.

The manifestations of the rheumatic diathesis are too frequently associated with digestive disturbances for the consistent physician to deny the intimacy of this relation, and it is not an uncommon thing for dietetic regulation, with attention to the inevitable defective elimination resulting from disturbed digestive activity, to bring about a complete control of the rheumatic phenomena. Certain it is that the excessive amounts of protein which are so commonly eaten combine with other factors to bring about the metabolic chaos which is so usually called rheumatism. Parenthetically, it might be remarked, these persons are not suffering from the results of mineral excess, although the laboratory evidence may seem to indicate this; rather they are undergoing their tortures because of a lack of the natural mineral elements—the vegetable alkalies—which the body needs, and which they could just as well have if their diet included more of such articles as potatoes, greens and cereals, and less meat.

Whether or no the initial cause is dietetic or bacterial in origin there can be no doubt that all forms

of rheumatism are evidences of essential changes in the chemistry of the body and, this being granted, should not the regulators of metabolism be considered both in the etiology as well as in the treatment of the various forms of this disorder?

It should be quite unnecessary to lend emphasis to the importance of the glands of internal secretion as regulators of the functions of the body. The hormones not only control, but correlate these various cell activities, and their work is so closely connected with the factors which are concerned in the reaction of the body to the causes of rheumatism, as well as to the attempts made to cure this condition, that the physician who considers the relation of the internal secretory glands and their hormones to rheumatism is more likely to solve some of its mysteries than the one who overlooks them entirely.

It is remarkable how close a relationship may be discovered between certain of the ductless glands and the symptoms which have come to be considered pathognomonic of rheumatism. Presuming for a moment that the various manifestations of the rheumatic diathesis are toxic in origin, is not detoxication essentially controlled by certain of the endocrine glands?

If the infective origin of rheumatism is admitted to be the most frequent or important, then we must also admit that certain of these remarkable organs are responsible for the production of the protective

measures which the body automatically brings into play in infections. Sir Almroth Wright himself insists that all the substances concerned in the control of infections must be considered as products of the internal secretory organs.

If functional digestive disturbances are the most common basis for this condition, then it is proper to consider the relation of the alimentary hormone, secretin, to this disease and, where digestive insufficiencies are manifestly present, recourse be had to the use of secretin as a remedy, for I am thoroughly convinced of its value as a physiologic means of stimulating lazy or inactive digestive glands, statements to the contrary notwithstanding. So whether rheumatic conditions are purely metabolic in origin, or whether they are due to micro-organisms, or to indigestion, we must not belittle the fact that in any event there must be a role that the internal secretory organs play which favors their prevention as well as the cure.

Under the present circumstances it would be quite difficult to consider this from the protective or prophylactic standpoint. Rheumatism is too insidious a disease. Its onset is of such a nature that it is not appreciated until one or more of the more definite manifestations—joint pain, immobility, swelling, etc.,—brings the patient to his physician. We can, however, make good use of this information in the diagnosis and treatment of rheumatic conditions. For example, too often the orthodox

treatment with salicylates or other neutralizing agents, does not give the desired degree of results, or merely tides the patient over whilst the disturbed chemical conditions are under the influence of the drugs or measures used. After a longer or shorter time the patient has a recurrence and unfortunately, too often it is more severe than the initial attack. In such cases the knowledge that the ductless glands may be frequently concerned in rheumatism will enable the physician to consider the case from a slightly different angle, one which I regret to say is rarely taken by the medical profession, and this new viewpoint may facilitate the control of future manifestations. It will also open up the possibilities of certain forms of organotherapy which, rightly applied, may materially influence the response of the organism to the other usual therapeutic procedures. Right here it should be emphasized that organotherapy is not recommended as the sine qua non in the treatment of rheumatic affections. Far be it from such, but as an important adjuvant and a phase worthy of consideration it deserves considerably more attention than it has previously received, as may shortly appear.

Leopold Levi, of Paris, insists that the thyroid is quite intimately connected with both the cause and, in certain cases, the successful treatment of various joint conditions, not excluding the most serious form, arthritis deformans, and in the intro-

duction to his recent book ("La Petite Insuffisance Thyroidienne et son Traitement") he makes the following statement: "Therapeutics is very helpful in the study of minor hypothyroidism for it reveals several stigmata of this condition which otherwise might be overlooked. For example, in March, 1905, we made the first application of thyroid therapy, aside from the treatment of myxedema, in a subject suffering with chronic rheumatism complicated with psoriasis. The first noted effect consisted in an increase in the appetite; the second result was a reduction in the marked feeling of cold which happened to be present (this sufferer was astonishingly cold and lived in a degree of heat that was altogether preposterous). Strangely enough the thyroid therapy made a marked diminution in this peculiarity and also benefited the rheumatism.

"The form of treatment applied in other cases of chronic rheumatism also directed our attention to a certain degree of benefit upon constipation." Elsewhere in the same book the author connects thyroid disturbances with rheumatic manifestations and quotes a large number of reports to the effect that "the reality of the thyroid causes of chronic rheumatism is incontestable. Its existence depends in many cases on thyroid lesions."

Chronic rheumatism is quite common in subjects presenting signs of hypothyroidism and it is well known that rheumatic manifestations may be associated with or aggravated by incidents in the meno-

pause. Frequently rheumatic manifestations follow thyroid atrophy due to pathological conditions or following thyroidectomy for Graves's disease, but the most important proof is the fact that the use of thyroid extract in many cases ameliorates rheumatic manifestations.

Thyroid therapy may be applied frequently in the treatment of various forms of arthritis with very good success. There are a number of papers recording and attempting to explain its remarkable results in various forms of chronic rheumatism. Probably the most comprehensive of all these communications is that of Leopold Levi who reports three hundred cases treated under his direction during a period of eight years. This investigator, who is well known to those who have read the literature on the thyroid gland, differentiates a form of rheumatism which is due to what he terms thyroid instability. The disease is found in relatively young persons, is only slightly deforming, and usually affects the smaller joints. It seems to progress by fits and starts. In these cases the joint disturbances are by no means the only troubles. Occasionally there are other manifestations of thyroid disorder sometimes evidently due to increased thyroid activity and at other times, the majority of cases it may be noted, the result of decreased thyroid activity.

The manner in which this form of rheumatism responds to treatment varies considerably with the

associated manifestations. In the juvenile form, where there is no very serious deformity, the response to treatment is good, and while the serious chronic and so-called "incurable" cases do not respond as rapidly to this treatment, there is no doubt that persistent thyroid therapy causes a very decided benefit. Levi concludes that in many cases of chronic rheumatism thyroid extract is "a precious remedy," securing an average of results that is very encouraging, and occasionally producing astonishing changes for the better. According to this writer: "Thyroid therapy should be placed in the first rank of the therapeutic armamentarium in the treatment of chronic rheumatism." He recommends a daily dose ranging from .05 to .30 grammes (1 to 5 grains) in divided doses. The average is  $1\frac{1}{2}$  to 3 grains per day and it must be continued for as long as six months.

The mechanism of the action of thyroid extract in certain conditions has for some time been in doubt; and this is especially true as far as its influence in rheumatism has been concerned. This extract, above all others, has been considered one of the best means of enhancing cell activities and increasing the metabolic exchanges. Since the metabolism in rheumatism is much below par, any advantage that accrues from thyroid therapy might be considered as due to this effect upon the cells.

A scientific explanation of this may be gathered from some interesting experiments by Slosse who

was professor of physiology at the University of Brussels before the war. He has carried out a number of experiments both in the laboratory and in the clinic to connect the disturbances of nitrogenous metabolism with the work of the ductless glands and as a result of his investigations he states that under normal circumstances the thyroid gland secretes a "hormone de desamination"—a deaminizing hormone—which influences the nitrogenous exchanges and when deficient causes a reduction of the power of the cells throughout the whole organism to split up the albuminoid substances, especially the nucleo-albuminoids, from which uric acid and other substances of the purin group are formed. Theoretically then, the enhancement of thyroid action should favor nitrogenous metabolism, and a large series of urinalyses made by Slosse and his associates substantiates this. The favorable clinical experiences which have been recorded by a number of French writers in a measure may be explained by these findings.

There is another form of chronic rheumatism somewhat similar to that which reacts to thyroid therapy. Like it, it is of endocrine origin, but instead of being due to thyroid insufficiency, it is a result of ovarian insufficiency. This is the rheumatism which appears in women after the menopause and it may be quite possible that its etiology is partly due to thyroid disturbances. At least it reacts more quickly to luteal therapy, especially if

this procedure is applied early in the course of the disease. Dalche reports that the administration of ovarian substance has given very good results in such cases, and in suitable cases he occasionally combines thyroid and luteal substance.

It is difficult definitely to state which case of rheumatism is of thyroid origin and which is not. According to Leopold Levi and de Rothschild the only way to answer this question is empirically to apply thyroid extract, and in explanation of this they may be quoted as follows: "From the practical point of view, in all forms of rheumatism in which the cause is unknown, it is an advantage to apply thyroid therapy. In such cases there will be more chance of results if the subject is young, if the rheumatism is accompanied by subacute exacerbations, and if there is only slight deformity. In those cases where there is a decided thyroid influence the initial results will be rapid, sometimes immediate. If the treatment does not act immediately, it is advisable to vary the doses, sometimes reducing them and giving the remedy for a longer period. There is no doubt that this medication may render very great service in the treatment of certain rheumatics, without exposing them to the least danger." Of course Leopold Levi looks at every disease from the standpoint of its relation to the thyroid gland—he has been called "thyroid mad"—but the fact remains that he and his associate, Baron Henri de Rothschild, are successfully treat-

ing scores of cases at their hospital with thyroid extract.

The thymus is another gland which seems to be connected in some way with the joint manifestations of rheumatism and several references have appeared in the literature in the last few years extolling the value of thymus extract in these chronic joint conditions.

Naturally, it is not always possible to cure the disease—far be it from me to hint anything as definite as this—but according to Nathan the first and most important beneficial change due to the thymus medication is a reduction in the pain present, and later, provided the case responds to the treatment, there is an increased mobility as well as a general betterment of the nutrition and health.

It is not yet possible to expain why thymus medication does this and in what mysterious manner these results are brought about, but we know, at least, that in early life the thymus controls in a considerable degree the mineral metabolism, for one recalls that thymectomy causes a remarkable softening of the bones and an obvious disturbance of mineral metabolism. It may be, therefore, that there is a principle in thymus extract which favors the re-establishment of the disordered metabolism of calcium salts which is undoubtedly a factor in these rheumatic cases, and that the benefit is due solely to this. Suffice it to say that in the treatment of arthritis deformans Nathan recommends

15 to 30 grains of thymus substance three times a day given for weeks or months and some very encouraging results have been reported.

In conclusion let us remember the intimate relation of the ductless glands to metabolism, the undoubted connection between rheumatism and metabolic disturbances and, therefore, the possibilities of organotherapy as a meritorious adjunct in the treatment of certain forms of rheumatism.

## XII

### THE RELATION OF THE THYROID GLAND TO EPILEPSY

THE study of the glands of internal secretion, now being taken up with avidity on all sides, bids fair to outrival many other phases of the study of medicine. Endocrinology has more to do with the really obscure and difficult problems of internal medicine than many have yet appreciated; and as our study becomes more thorough we are realizing the extremely intimate relation between the endocrine organs and practically every phase of physiological activity. We are learning to appreciate as never before the importance over all of the body of the chemical effects produced by the hormones from these glands.

To me the most interesting and recent work on so-called "idiopathic epilepsy" (the only form of epilepsy referred to in this paper) is that of C. A. L. Reed, (1) of Cincinnati, whose several communications have emphasized three important considerations: 1st, that intestinal stasis is almost without exception present in epilepsy; 2nd, that a prominent result of the associated toxemia is a varying degree of acidosis which produces a condition of edema of the brain to which a part, at least, of the

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1916.

characteristic manifestations of epilepsy are due; and 3rd, that in operating in the manner of Lane on cases with pronounced intestinal stasis, a marked infiltration of the peritoneal and mesenteric glands is usually encountered, and that from these glands an organism, named by Reed the epileptococcus, frequently may be isolated.

Though I do not question the findings of such an authority, I may be permitted to have an opinion as to the fundamental causation of the stasis, the acidosis, the edema and the glandular enlargement. For the moment I am not interested in the bacterial findings and the suggestion that we may eventually work out a vaccine therapy for this disease.

I believe that in every case of epilepsy there is a distinct endocrine element which is present and prominent much more frequently than has been admitted in the literature on the subject. This will be discovered to be as early and constant a clinical manifestation as any others with which we are better acquainted at present.

The principal organ of internal secretion involved is undoubtedly the thyroid gland, although others, notably the pituitary, gonads and parathyroids, have been connected with the clinical findings of epilepsy.

It may be well to reiterate some facts concerning the relation of the thyroid to the picture of intestinal stasis. The man to whom we are indebted for first directing our attention to the minor form of

thyroid insufficiency, Eugene Hertoghe, of Antwerp, and who is still the leading student in this line, called particular attention to a syndrome identical with that so prominently brought to the fore by Sir Arbuthnot Lane, and did it nearly twenty years ago! Quoting from a recent resume of his work (2) on "chronic benign thyroid insufficiency" or "myxedeme fruste," we read:

"The entire gastro-intestinal system reacts very strongly to the infiltration of its elements, whether muscular, nervous, secretory or mucous. Infiltration of the muscular tissues induces peristaltic paresis, leading to retention of waste materials with consequent fermentation and constipation. In delicate subjects with weak abdominal walls this results in ptosis of the viscera, notably of those organs which are most heavily loaded, namely, the stomach and large intestine. . . . Imperfect intestinal drainage gives rise to intestinal toxemia, which reacts upon the already enfeebled thyroid and intensifies the prevailing conditions of inadequacy. As a matter of fact, many of the symptoms attributed by Lane to chronic intestinal stasis are identical with those which, since 1899, I have included in the symptom-complex of benign chronic subthyroidism. These are hypothermia, uncontrollable headache, rheumatoid pain and neuralgia, mental depression, dyspnea, asthmatic attacks, premature grayness and baldness, dental caries, cholelithiasis and brownish pigmentation of the skin."

It should not be difficult to demonstrate a further relation between the thyroid and epilepsy. The insignificant, but none the less important, signs of the slighter form of dysthyroidism are very commonly found in epilepsy, occasionally one or two of them being very well marked, or again, several of them together but not especially definite or obvious. This is the usual reason that the thyroid element is overlooked; but when one is careful, some of these signs will be found. The permanent or transitory edema or infiltration of various tissues results in such widely differing symptoms as nasal obstruction,\* changes in the voice, headache, migraine, a dry, rough skin, thinning of the hair and especially the outer third of the eyebrows, coldness of the extremities, abnormal chilliness, dullness and backwardness, menstrual disorders, etc.

These symptoms, together with those mentioned in the above quotation from Hertoghe, include a majority of the clinical findings of hypothyroidism. While it is not possible here to go into the whole subject, we must mention the frequency of dyscrasias in other ductless glands in epileptics, especially of the gonads, for it is well established that there is a distinct connection between puberty and

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\*There are numerous incidents on record in nose and throat literature which indicate that when deflected nasal septa and other obstructive conditions of the nose and throat have been surgically removed, there has been a coincident benefit as regards the number and severity of the epileptic seizures. Many times these obstructions are not altogether organic, and when the mucosal infiltration is associated with thyroid insufficiency and is removed by thyroid therapy, the results are equally good.

the menses, and epilepsy. It is common to find that some menstrual irregularity, or even what appears to be the normal menstruation, seems a signal for the onset of a seizure. Hundreds of cases have been seen in which a decided ovarian element was present, and, in most of these, I am sure that there has been an equally prominent thyroid disturbance which many times was responsible, in part at least, for the epileptic and the menstrual disturbances.

In passing, I might mention an interesting and somewhat confirmatory report by Weeks and Renner (3) on a case of Raynaud's disease associated with epilepsy. Within the past year, no less an authority than Oliver T. Osborne, (4) of Yale, has shown that the several vasomotor disorders, of which Raynaud's symmetrical gangrene is the extreme type and chilblains is a lesser type, are always associated with thyroid disorder, although other ductless glands may be simultaneously involved.\* According to Osborne, thyroid therapy, judiciously employed, causes improvement in most cases of Raynaud's disease and some cases are actually cured.

There is something more than incidental in the relation of the alimentary conditions in epilepsy to

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\*Let me mention here, parenthetically, that it is practically impossible to have a disorder of the endocrine glands involving a single gland of internal secretion. Their hormonic relation is so intimate (or as McCord has so well expressed it, the glands of internal secretion constitute an "interlocking directorate which controls the body"), that uniglandular disorder invariably means a pluriglandular complex.

those we may expect in chronic hypothyroidism. In epilepsy it has long been recognized that the tendency to constipation invariably present (despite the fact that we are often told that "the bowels move quite normally") complicates the disease by aggravating the intensity and frequency of the seizures. It is now universally known that one must always give special care to the bowels, irrespective of seeming normality, and also cut down the protein intake, especially the amount of meat. In hypothyroidism, also, a similar form of constipation is the rule. Leopold Levi, (5) the greatest French authority on thyroid dyscrasias, lays emphasis on his opinion that constipation of thyroid origin is frequent and, perhaps, is the most frequent form of constipation.

Both epilepsy and thyroid disorders very commonly have an hereditary predisposition underlying them. Cretinism, of course, is not an acquired disease, and the hereditary tendency to thyroid instability is one of the easiest to trace back of all of the factors present. I need only remind you of the frequency of thyroid instability in the children of parents, and especially mothers, with irregularities of the ductless glands, or mention the well-known fact that an undue strain upon the thyroid apparatus prior to or during pregnancy is the most usual basic cause for many of the varying degrees of thyroid inadequacy that we discover almost every day if we look keenly for them.

Thom\* studied 157 cases of epilepsy quite recently and found that no less than 126 showed a direct hereditary connection—either a parent or a grandparent had the disease. In thirty-eight per cent. of the series studied, epilepsy was associated with alcoholism—one of the commonest causes of acquired or transmitted functional or organic endocrine disorders. Mental disorders were present in twenty-seven per cent. of the parents of these cases and feeble-mindedness in more than ten per cent. We need not more than mention in passing that one of the most frequent causes of feeble-mindedness is thyroid disorder, and that insanity has been connected by numerous writers with disorders of one or more of the ductless glands, usually the thyroid or the ovaries, as often as with any single condition. Still further, I am confident that some day it will be better understood that the two most prolific causes of insanity—syphilis and alcoholism—bring it about by their insidious disorganization of the work of the glands of internal secretion, more than in any other manner.

There are various communications in the French medical literature, to which reference should be made. Gauthier (6) has collated many, and supplements them with several personal case reports. He finds that thyroid therapy is a helpful measure in epilepsy, especially where other evidences of thy-

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\*Figures quoted from editorial in Ellingwood's Therapeutist, 103 (1916).

roid insufficiency are present. It may be well to translate a few lines from his book:

"Epilepsy is considered by a large number of physicians and neurologists to be an intoxication, or a general disorder of metabolism. There is also a possible connection in certain cases with the work of the thyro-parathyroid combination. The association of epilepsy with myxedematous idiocy, cretinism and even Basedow's disease is well known. But there are other evidences. Many cases of simple goiter become epileptic and goiterous mothers give birth to epileptic children (Rapp, Jeandelize, Parhon, Goldstein, Hertoghe, etc.). Claude and Schmiergeld, (7) in a study of seventeen cases of epilepsy from the endocrine point of view, have found in every case alterations in the thyroid gland and in twelve of these the structure of the gland was completely altered with areas of sclerosis and limited zones of compensatory hypertrophy of the glandular tissue. . . . Parhon (8) examined the thyroid in twelve epileptics. He found it smaller than usual and showing frequent and variable histologic changes, and, interestingly enough, the iodin content was very often increased."

The cerebral edema which Reed and Martin Fischer of Cincinnati are now convinced is a result of the toxic acidosis, is just as likely to be of thyroid as of intestinal origin, for not only may the acidosis or systemic hypoalkalinity result from the

loss of the full effective hormonic service of the thyroid, but the essential infiltration,\* which is the typical pathognomonic feature of hypothyroidism affects all the tissues of the body, for the thyroid exerts a cellular influence which is not limited to any organ or set of organs, hence, not only the brain, but also the peritoneal and mesenteric glands may be infiltrated as noted by Reed and mentioned in the beginning of this paper. In this connection it may be well to state that Hertoghe (9) has described a form of coma of thyroid origin in which one of the constant findings on autopsy was an infiltrative edema of the brain.

A certain well-defined fact, first set forth by Hertoghe and later by Leopold Levi, enables us to give a final emphatic demonstration that the position held regarding the importance of the thyroid element in epilepsy is not untenable. Benefit from thyroid therapy can not be expected in the numerous conditions for which it is given unless there is a definite need for the chemical substances or hor-

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\*The most marked result of the loss of the thyroid hormone is a condition of cellular inactivity and mal-elimination. This results in a peculiar form of infiltration which may affect any cells that are under the influence of this gland. This means practically all forms of tissue. This infiltration is best recognized in the puffy, dough-like skin of myxedema, and while it may not be so marked, it is the principal cause of the majority of the manifestations of thyroid insufficiency. One can readily understand that the obesity, stiffness of the muscles, ligaments and joints, intestinal sluggishness, and in fact, disturbed cell activities in general, including the brain, nerves and tissues generally, may be thus referred to a more or less well-marked metabolic inactivity which follows the loss of the essential hormone stimuli which the thyroid sends to every part of the body.

mones thus administered. In Levi's words (10): "When the results of treatment with thyroid extract are immediate, continued, constant or pronounced, they may be regarded as a diagnostic factor." Hertoghe tells us the same thing in other words: "If certain patients are carefully examined, they will be found to show symptoms of general thyroid insufficiency, and this is invariably the case with those who derive benefit from thyroid medication."

There are not a few reports from which we may gather that empirical thyroid therapy has exerted some beneficial effect in epilepsy. I have noticed this a number of times myself, though I should not want to imply that the benefit was solely due to the thyroid medication. Many of us, perhaps, have given this remedy in anticipation of a possible benefit just as we have come to expect, somewhat unscientifically it is true, that thyroid extract may help a host of widely differing conditions. These scattered results are among the best reasons for applying the etiologic, diagnostic and therapeutic principle which I am discussing. When applied systematically in the routine treatment of epilepsy in which one can find clinical evidence of hypothyroidism, accompanied, of course, with such other curative and symptomatic treatment as the exigencies of each case demands, the prognostic prospects should be considerably better.

With these opinions in mind, we are justified in

drawing some conclusions which seem to have a reasonable bearing on the subject under discussion:

1. That thyroid insufficiency is likely to be a frequent underlying factor in the etiology of epilepsy for several reasons: (a) It favors toxemia; (b) it produces cellular infiltration and edema, which may affect the brain in the manner described by Hertoghe, Reed and others, and (c) it usually causes other symptoms in epilepsy which have been definitely attributed to hypothyroidism.

2. Hence the study of epilepsy from the standpoint of the glands of internal secretion is rational and worth while.

3. Thyroid therapy is a rational therapeutic adjunct in the treatment of epilepsy accompanied by other signs of hypothyroidism.

4. Favorable results from the use of thyroid extract in epilepsy should be considered as a confirmation of these conclusions; and an incentive to further clinical study in this direction.

In closing I do not want to leave the impression that a few weeks of thyroid therapy will cure epilepsy. Rather do I wish to emphasize that the thyroid gland, because of its intimacy with detoxication and metabolism in general, deserves to be considered in the investigation of every case of epilepsy; and where one finds other evidences of waning thyroid sufficiency, thyroid therapy may be instituted in conjunction with other rational treatment, and a better percentage of results be attained.

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## XIII

### THE DEFECTIVE CHILD FROM THE STANDPOINT OF THE INTERNAL SECRECTIONS

DEFECTIVE children, or "children requiring special attention" as a colleague appreciative of the sensibilities of the parents calls them, are practically without exception endocrine cases.

There are several comprehensive classifications of defectives; and the methods of measuring their physical and mental capacity, or lack of it, enables us to place a given case in the same class as others affected in a similar degree. This, however, does not indicate the etiologic factors influencing the child and, hence, the proper treatment.

It is true that children handicapped with hereditary syphilis, epilepsy or any transmitted disease or disease tendency, more often are considered as syphilitic or epileptic rather than as suffering from dyscrinism. Nevertheless the fact remains that in all such cases the endocrine element is both present and prominent irrespective of the simplicity or complexity of the trouble and its cause.

With our present knowledge we may safely say that the treatment of defective children offers better prospects of success than ever before. Of course

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what is known as feeble-mindedness or amentia may be more than a mere "deficiency," for the cerebral development may be imperfect and here there is little or no hope for a successful outcome.

In the past few years considerable interest has been aroused in the relation of endocrinology and the study of defective children; and it is surprising how many of the stigmata which cause us to place children in this category are connected with abnormal endocrine function and, too, how frequently on investigating their antecedents we uncover a more or less well marked endocrine disorder in the parents or grandparents which properly may be regarded as a part of the cause of these unfortunate conditions in their offspring.

The hereditary phase of the relation of dyscrinism to defectives will be referred to again later as it seems to be a hopeful phase of a very hopeless subject.

It will be my endeavor here to lend emphasis to the importance of considering this subject from the chemical rather than the physical standpoint, and to secure more attention by readers to the study of the ductless glandular manifestations, obvious or insidious, in defective children.

There are almost as many forms of developmental anomalies in children as there are glands of internal secretion. Chief among them all are those relating to dysthyroidism. The cretin, well known to be typical of a large class of deficient, is an

endocrine case pure and simple, the syndrome being definitely traced to deficient thyroid activity and, fortunately, being decidedly benefited by substitution therapy or the administration of the missing chemical substances. In fact a large part of our first knowledge of the clinical importance of dysthyroidism resulted from the studies of George Murray, Sir William Gull and Theodore Kocher some twenty-five years ago upon individuals who were all in one way or another mentally and physically defective.

The literature upon the retarded, backward or deficient child recently has begun to contain references to the syndrome "hypoplasia" and according to Noble (1) the hypoplastic individual is one whose nutrition and development is below par, the condition being congenital or acquired during infancy or early childhood. There are varying degrees of hypoplasia reaching from backwardness which is not appreciated until the child has been some time in school, to the serious organic dyscratism which is sometimes called infantilism and sometimes mal-development.

It is difficult to say how much of the symptomatology of this condition of hypoplasia may be referred to the thyroid gland. Much of it at least is of thyroid origin and Hertoghe (2) refers to it frequently in his writings and uses the term "thyroid inanition" as indicating a condition of slow starvation and inactivity without particularly ob-

vious changes in contour or weight. Function, however, is much below par and it is but a short step from the unappreciated "forme fruste" of thyroid insufficiency to the myxedematous idiocy described by Brissaud, or the Lorain type of infantilism, in the former of which mental development seems to be more definitely affected while in the latter the mind is clear and capable and physical development is deficient.

Hypoplasia in children according to E. B. McCready of Pittsburgh, who is a close and intelligent student of this subject, properly may include the backward child "who is retarded in his development by reason of some condition either inherent in the child himself, which can either be removed or counteracted, or who is subject to some physical defect or environmental condition, the removal of which will allow him to progress in a normal manner under favorable opportunities." (3)

From the standpoint of this author, with whom I am heartily in accord, the hypoplastic child is not necessarily a sufferer from an unchangeable developmental complex. The stimuli to growth and development have not been sufficiently strong and these necessary manifestations are at a standstill or below par. Fortunately this class constitutes a large proportion of the so-called "backward children" and from a clinical standpoint the prognosis has been radically changed for the better since the advent of scientific endocrinology and a better ap-

preciation of the possibilities of substitution therapy.

The hypoplastic individual is suffering from an arrested development. All function is at half-speed or even slower and among the early symptoms enumerated by McCready (4) are: Delay in the power of walking and talking, late closing of the fontanelles, irregular dentition, though progress in these respects may be entirely normal and even more rapid than normal for the precocious child is often an hypoplastic one. Additional early signs are nocturnal enuresis, the so-called scaphoid scapula, a tendency to lymphatism with adenoids and hypertrophied tonsils, and pronounced malnutrition.

Leonard Williams (5) has brought together enough clinical and therapeutic evidence to establish the fact that enuresis in the hypoplastic child is largely a result of thyroid insufficiency, which is so commonly present, and the successful administration of thyroid extract in these cases tends to bear out this contention. Incidentally Williams believes that adenoids and enlarged tonsils represent a compensatory action of the body, tending to counterbalance the thyroid insufficiency.

Graves (6) finds the scaphoid scapula so common in these cases that in a report of 47 children who were behind in their grades, all were under size and showed various anomalies in development, 58 per cent. were mouth breathers, 17 per cent.

were subject to enuresis and 85 per cent. showed the scaphoid scapula. Another fairly constant symptom, according to McCready, is the high-arched palate which is presumed to be produced by the yielding of the palatine bones owing to their relative deficiency in calcium. Enlarged tonsils and adenoids, while common enough, are more likely to occur in hypoplastic children and according to Noble (1) this pathological condition of cell hypoplasia explains the reason for a large group of debilitated women and also all the children who are not vigorous and who have adenoids and diseased tonsils and who become mouth breathers.

It is not possible within the limits of this brief communication to mention a tithe of the statements in the last ten or fifteen years regarding the endocrine basis of developmental disorders in children, but if the students of these "children requiring special attention" will look carefully for the functional accompaniments of thyroid insufficiency\* (7) they will be found in a large proportion of the cases.

Probably the next most important gland that deserves study in this class of cases is the thymus, for thymus enlargement or in older children the persistent thymus, is found to be very commonly connected with disorders of this character,

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\*To avoid repetition the reader is asked to read Chapter IV in this connection and especially the symptomatology of hypothyroidism as outlined on page 38.

just as a premature atrophy or absence of the thymus also may be found. Hard and fast statements can not yet be made as to the real function of this gland. Some deny its internal secretory powers and call it merely lymphoid tissue. Not all are unanimous about the relations of this gland, but from a clinical standpoint, I am certain that the thymus is involved in many cases of this character for I have personally demonstrated an enlarged thymus in a number of children that have come to me for diagnosis or treatment and following a fluoroscopic examination I have had these children irradiated and later on re-examination have discovered a considerable reduction in the thymic shadow which was accompanied by benefit to the symptom complex under treatment (though of course I admit that this procedure just mentioned was but a part of the treatment).

There is no question about the defectiveness of children suffering from the well-defined status thymico-lymphaticus, though mentality may be normal. In such cases an early diagnosis may be facilitated by a differential blood count in which the lymphocytes will be found to be greatly increased (100 per cent. or more). There will be hyperplasia of various groups of lymph glands as well as the tonsils and spleen and the skin will have a pale, badly nourished appearance and occasionally there will be an associated mal-development of the genitalia.

Thymus hyperplasia in children is usually accompanied by the "hypoplastic state" referred to before. The increased cellular growth of the thymus and other lymph structures is modifying the chemistry of the body in such a way that the deficiencies of hypoplasia are permitted to show themselves. These individuals are of the flabby, semi-obese type and practically always have other evidences of developmental dystrophy. Occasionally in addition to the osseous changes already mentioned (high arched palate and scaphoid scapula) the bony development is modified seriously, the epiphyses are late in joining and rickets may be present.\*

On the other hand, Bourneville has shown from a large series of autopsy findings that over 70 per cent. of mentally defective and epileptic children have no thymus at all. This may seem to be contradictory but it is none the less suggestive as it directs attention to the thymus as a regulator of the chemistry, and whether deficient or excessively active, it is a factor deserving of our study.

While it is granted that our knowledge of the thymus gland is none too definite as yet, we are safe in assuming it to be an important factor in defective children, and initiating a careful physical examination for the gland itself and a search for

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\*A number of writers indicate a clinical connection between thymus disorder and rickets; and the subject is considered from the standpoint of treatment in the prize article which constitutes Chapter XVIII.

evidences of dysthymism. If this search is unremunerative it is a great advantage to me to have ruled out the likelihood of thymic involvement for not infrequently it is present and ignored altogether with obvious detriment to the success of the best of treatment.

Still another gland is prominently identified with developmental disorders in children. The hypophysis or pituitary has much to do with the chemical control of development and while it may not be so important as the thyroid it is more important than some have thought. Quite the most important recent step in the development of our knowledge of the ductless glands is the discovery by T. Brailsford Robertson of the University of California of the active principle of the pituitary gland proper, tethelin, and its growth-controlling function. (8) It is entirely possible that in tethelin we may find a most useful means of stimulating deficient growth though to date the use of this principle has been largely limited to the laboratory. So far I have used the desiccated anterior lobe of the pituitary in fourteen cases with advantage in enough to establish my confidence in this form of treatment. Suffice it to say that many deficiencies in children have a pronounced pituitary origin and it is a routine in my work to study all such children from a pituitary standpoint. Radiographs of the sella turcica are made, and quite often I have found obvious changes in the shape and size of the pitu-

itary fossa. An interesting case is already mentioned elsewhere in this book\* and while pituitary feeding is being practiced more frequently, too often I am finding that this has been done in cases coming to me for consultation, without any accurate reason therefor and naturally without good results. I have in mind a case of developmental dystrophy that had been treated for many months first with thyroid and then with pituitary and then with both, without the slightest beneficial results. The case was none the less one in which gland feeding was in order, but this was not successful until given with reason and accompanied by such adjuvant procedures as needed to be carried out simultaneously. In other words, it is bad policy to treat symptoms instead of patients, for not infrequently such treatment is unsuccessful and the interest of physician and parent in this is lost when in reality it is the only hopeful thing.

Pituitary infantilism is very completely studied and illustrated by Cushing and his monograph\* is the most comprehensive piece of literature on the subject extant.

The adrenals likewise may be involved and adrenal sensitiveness is not uncommon in defective children. Slight psychic or emotional stimuli make a very great impression on them. They fatigue

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\*See Chapter V, page 58.

\*The Pituitary Body and Its Disorders, by Harvey Cushing, J. B. Lippincott Co., 1912, Philadelphia.

easily and the cardio-vascular tone is low. I have noted a number of times a peculiar bluish mottling of the skin, especially of the lower parts of the body and a tendency to dermographia, which I have laid to some adrenal element in the pluriglandular disturbance. These circulatory-cutaneous manifestations may not be of great diagnostic significance *per se*, but they are of value as indicators of a prospective dyscrinia and a means of stimulating further study of the endocrine functions.

Already considerable emphasis has been laid upon the importance of pluriglandular dystrophies and I may say that I have never seen a defective child in which there was a pure monoglandular disorder, and I do not believe there ever has been such a case. The reasons for this have already been quite fully discussed elsewhere in this book and the obvious therapeutic indication is to be sure that our treatment is comprehensive.

McCready\* in his work along this line has devised a combination of glandular extracts which he has had prepared for him by Messrs. Burroughs,

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\*I think it is only proper to give much credit to Dr. McCready for the aggressive and intensive way in which he has studied what he chooses to call "pedology." He has unusual facilities in the Children's Courts at Pittsburgh and also his institution "Wildwood Hall" offers ideal facilities for the suitable care of children requiring special attention. The successful treatment of this class of cases involves not merely glandular feeding but intimate hygienic and dietetic control, special education and an ideal environment; and it is almost impossible to secure these at home or in most institutions in which such cases are handled by the State.

Wellcome & Co. This is now obtainable in trade under the name "Tabloid Mixed Glands" and to my mind this is a much more satisfactory treatment than the single extracts which we have been wont to use in the past, and it has the advantage of enabling one to stimulate the endocrine system as a whole rather than a part of it; and where necessary, by adding additional amounts of such other extracts as may seem to be indicated, special homo-stimulation may be brought about.

It would not be proper to dismiss the subject without considering a phase of it which is deserving of much more concerted study and action. Not a little concentrated attention has been directed at the huge task before the medical profession of preventing as far as possible the dire results of mental and physical defects and diminishing the extent of this most pitiful of all phases of social medicine.

Perhaps the most reasonable and practically interesting communication on this subject is the address by Sajous (9) in which he makes a plea for co-operation along a line which is altogether new. Sajous brings sufficient evidence to show that glandular insufficiencies of a minor character in mothers are likely to be impressed upon their unborn offspring and the obvious thing to do in cases of this character is to be sure that these insufficiencies are minimized at the time when this treatment will offer the greatest prospects of results. In other words, if a mother is suffering from thyroid

insufficiency it is likely that her child will have leanings in the same direction and thyroid feeding is in order during pregnancy. I have personally discovered in scores of cases a very clear relation between ductless glandular disturbances in the mother and her offspring. In fact it is almost the rule to find that the woman with a goiter transmits a tendency to goiter to her daughter and when patients come for treatment the history will show almost always a hereditary basis for troubles of this character.

I can do no better than to select a few weighty sentences from Doctor Sajous' address, as by reprinting them a greater appreciation of this subject may be stimulated:

“Any disease capable of injuring the ductless glands sufficiently to inhibit their functional activity impairs correspondingly the development and functional activity of the brain, by reducing the supply of secretions this organ requires to carry on these physiological processes.”

“The main underlying cause of defective mentality in both parent and offspring is inherited deficient activity of the ductless glands.”

“We should start a campaign having in view the salvation of these unfortunate infants by supplying, through the intermediary of their defective mothers, and, after birth, through their food, the secretions they lack to complete their development.”

"In the majority of functional cases of feeble-minded and backward children met in current practice, the predominating pathogenic factor is hypothyroidism, though deficiency of other internal secretions is also discernible in most instances."

"On the whole, the intimate relationship between the ductless glands and everything that concerns reproduction, the greater relative size of these organs in the product of conception, and the teachings of practical experience in organotherapy, all tend to indicate that whenever the father or mother is a mental defective, or both parents show any sign of deficient activity of one or more ductless glands, or are mental defectives, organotherapy should be instituted as soon as pregnancy is recognized."

"The mental and physical status of all pregnant women as regards the functional efficiency of their ductless glands, which may be determined by the stigmata of deficiency of these organs, should invariably be established. If found deficient, organotherapy should be used to protect them against renal disorders and convulsions through toxemia, and also their offspring against imperfect development and mental deficiency."

In closing I feel to add that the foregoing statements are deserving of the closest attention, and that the principle so clearly enunciated applies to all deficient or defectives and not merely to those in which the mental element predominates.

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## XIV

### ORGANOTHERAPY IN CHRONIC DISEASE WITH SPECIAL REFERENCE TO ITS POSSIBILITIES IN CANCER

THE treatment of chronic disease, at best too often a difficult and unsatisfactory matter, has been considered by so many physicians so many times that further reference to the subject may seem to be almost out of place, for already there is an overwhelming number of papers and many books concerned with the advantages of all forms of treatment of chronic disease, from the surgical removal of presumably offending organs to the Emanuel Movement, and including other more or less useful methods such as hydrotherapy, electrotherapy, psychotherapy, serotherapy, autotherapy, and, most recent of all, the intestinal short circuit as suggested by Sir Arbuthnot Lane.

The mere fact that disease has been present for more than the proverbial forty days and that a good percentage of chronic invalids perambulate from one doctor's office to another, as well as the suggestion already made that many widely differing forms of treatment are advanced more or less enthusiastically from time to time, seem to be con-

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vincing evidence that the treatment of chronic disease is still an unsolved problem and hence worthy of persistent study.

This evening it is proposed to consider another fairly well known phase of therapeutics and to urge its more frequent application to the indefinite and chronic disorders, many of which have not the dignity of a name and others of which are classed, rightly or wrongly, under the name of the principal symptoms, chief among these being neurasthenia. It does not seem advisable, at this stage of progress, to make any hard and fast statements, hence all that may be said here to-night will be purely suggestive, the prospective value of such procedures as may be mentioned being left to the judgment of those who, being convinced of the reasonable basis outlined, may be sufficiently interested to put them to the test.

There seem to be fashions in medical matters just as there are in dress or art. If I am not much mistaken it is beginning to be the fashion to study and write about the internal secretions. A number of books have appeared on this subject. I even plead guilty to having written one on the therapeutics of the internal secretions. There are, without the least exaggeration, thousands of papers on the various phases of this fascinating subject published in practically every quarter, chiefly however in French, Russian, and Italian.

All this is as it should be, for from all sides come

words of commendation and evidences of profound interest, and every interested physician that I have had the pleasure of meeting in half a dozen different countries has manifested an unwonted enthusiasm in his investigation of this subject—it breeds enthusiasm, for so often we stumble across the most startlingly wonderful things which when they are first published abroad are usually greeted with the smile of scorn, just as were Roentgen's remarkable rays, or Marconi's equally amazing discovery, or Alexander Graham Bell's wonderful invention, by which all of us have profited so much. Sir William Osler told me only a short time ago when I visited him at Oxford that surgery had been having its innings for the past ten years or more and it was time for medicine to have its turn and probably the "bat" would be the internal secretions of the ductless glands. For instance, what surgical discovery excels in its scope and wonder the many-sided usefulness of pituitary extract?

In these days of advance in physiological and pathological research we have gradually accumulated a fair knowledge of the series of organs which were until recently almost entirely unknown. We have learned that the ductless glands or endocrinous organs exercise an intimate control over metabolism and the cellular activities, that this is in all probability brought about by definite chemical substances produced in these organs and conveyed from them to others by means of the blood and

lymph—the “hormones,” so named by Starling in 1902—and, best of all, that it is possible to secure from animal glands certain active hormone-bearing substances in a more or less pure state which are available in the treatment of the disease.

We cannot stop to consider the occasional statements to the effect that organotherapy is a fad, or that it is still in its infancy and hence not worthy of more than passing consideration, and that much more work will have to be done before the subject reaches a really practical stage. Those who manifest such sentiments invariably make their statements without deliberation and due consideration of the facts. None can deny that certain of the ductless glands produce extremely active principles which have an equally active influence in the control of normal as well as morbid phenomena. We have only to recall the influence of thyroid extract in myxedema, adrenalin in local hemorrhage, or pituitary extract in labor to realize that there are sufficient inducements to delve more deeply into the study of the extracts of these organs, as well as of others known to be concerned in the maintenance of what is now termed “the hormone balance.”

This factor deserves much more consideration than it is possible to give it this evening, for the delicate balance brought about by the interrelation of the internal secretions is concerned in the maintenance of essential health none the less than in

the production of deviations therefrom. I am going to propound what I believe to be an axiom—it is impossible for an individual to manifest the results of chronic disease without a corresponding disturbance in some or all of these hormone-producing organs. Further than that, I believe that many of these intractable symptoms-complex, to which it is sometimes so difficult to give a suitable name, are often aggravated by a disturbance in what has been termed the "altruistic function" of the cell. I will explain: Campbell considers that cell activity is properly divided into the egoistic and the altruistic cell functions. The former consists in the maintenance of individual cell activity, while the latter concerns the supply to the organism as a whole of certain services, probably brought about by the hormones, such as are exemplified in the numerous functional relationships between organs. This altruistic function is of extreme importance, for the cell itself may seem to all intents and purposes quite healthy and yet still gravely fail in its altruistic functioning—a failure which, small though it be, may suffice to disorganize the delicate hormonic balance. Granting, then, that chronic disturbances are associated with general cellular inactivity and that in certain conditions this deprives the body of essential stimuli, it must be obvious that the effective treatment of such conditions must include a consideration of the ductless glands and of means capable of re-estab-

lishing the normal production of their hormones.

One of the most common disorders in which so-called "pluriglandular insufficiency" is evident is neurasthenia, in which there may be no positive evidence of defective action of a gland or series of glands. It is obvious that in the majority of such cases there must be a disturbed endocrinism, for it is hardly reasonable to suppose that in an individual with prominent manifestations of half-speed function, such as constant fatigue on slight exertion, defective oxidation as evidenced by low urinary solids, nerves that are easily set "on edge," circulation that is poor, with cold, clammy extremities, and not infrequently reduced tension, ambition and mental powers much below par, and the like, the production of the essential chemical messengers is not reduced just as are all the body activities. This being the case, pluriglandular therapy not only serves to replace, in however slight degree, the missing secretions, but favors an increased production of them by the homostimulant action already referred to.

Theoretically this sounds very plausible and practically it has been found to work very nicely. Pluriglandular therapy is undoubtedly empirical, for in the class of cases under discussion at least, there is no definite proof as to which of the ductless glands is deficient and to what extent. For this reason it has been ridiculed by some who forget that nine-tenths of our present therapeutics was at

one time purely empirical, while a good share of it still has no positive scientific basis. A procedure that has secured results before may do so again, hence it is worth trying. This is the present position of pluriglandular therapy, and it is believed that the successes already obtained are an earnest of what is in prospect.

Another important series of chronic conditions which must at least be mentioned in passing are the functional neuroses and psychoses, many of which are now earmarked as resulting from or being intimately associated with disordered secretory action of certain of the ductless glands. In a recent paper in the American Journal of Insanity, Murray Auer concludes that the glands of internal secretion mutually influence functional activity and the occurrence of insanity at puberty and adolescence, after severe physical and mental strain, and at the time of the menopause (all periods when the metabolic changes of the body are intense), and the occurrence of syndromes unquestionably the result of disease of the endocrine organs, insanity, idiocy, debility, mania and dementia, suggest strongly that the true etiology of the affective psychoses lies in functional disturbances of the glands of internal secretion.

Many of the problems of the medical gynecologist have an altogether endocrine origin, and the metabolic disturbances of women constitute a large class of chronic diseases in which organotherapy is

an extremely useful measure. Substitutive organotherapy is an every-day measure of the most progressive gynecologists and the subject is far too large to discuss here. The value of the extracts of the corpus luteum in ovarian hypofunction, as well as the homostimulant action of the same substance in less serious conditions, is becoming increasingly apparent. Pituitary extract is now used in a great many cases of this class, not merely for its obstetrical virtues but as a means of re-establishing a disturbed balance in cases like amenorrhea and certain forms of dysmenorrhea.

One of the most neglected organotherapeutic remedies in gynecological practice is the extract of the mamma, about which I cannot refrain from saying a few words. Briefly, the mamma is also an internal secretory organ and is the direct antagonist of the ovaries, hence extracts thereof may be of value in the control of conditions due to superactivity of the ovaries. The principal among these are menorrhagia, metrorrhagia, and uterine fibroids. I know the surgeons will disagree, but the fact remains that functional uterine hemorrhage (not due to foreign bodies or organic conditions) is frequently controlled better by a course of mammary extract than by any other means and there is a rational physiological reason for this benefit. A number of Russian investigators have shown that the use of mammary substance is of extreme value in many cases of fibroids and those

who may be especially interested in this subject might with an advantage read a paper which I have prepared for a Special Internal Secretion Issue of the Woman's Medical Journal for March, 1915.\* Suffice it to say that enough evidence is gathered together there to warrant the use of mammary extract for a period before operative procedures are taken and the aggregate results are sufficiently good eventually to bring this method of treatment into much higher esteem and frequent usage.

[Within the past year (1917) I have had occasion indirectly to note the clinical value of this phase of treatment in a case of well-advanced cancer. A colleague, interested in organotherapy, was recommended to try mammary substance in a case of uterine carcinoma in an old woman. There was much hemorrhagic oozing, as well as very bad odor. Twenty grains of mammary substance were administered each day for a week and the dose then increased to 30 grains. The treatment was suggested by me in the hope that the oozing which had persisted for months despite various internal and local treatments, might be staunched. I was particular to emphasize the slimness of the prospects and that the method was really offered as a last resort.

Not only was the hemorrhage stopped but the odor was considerably diminished and the patient

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\*See Chapter XVI.

even began to assure her family that she was going to get well, since her strength really did improve quite considerably. The doctor, however, took pains to inform them that the treatment was merely having an effect upon the blood supply of the affected organ and not upon the disease itself, and even so this seemed to all concerned to be a very distinct vindication of the anti-hemorrhagic effect upon the uterus of mammary substance.]

You will note that I have said nothing about the use of thyroid extract in the chronic and well-known conditions associated with thyroid deficiency, nor can I take time to outline the advantages of pituitary extract in those equally chronic conditions of hypopituitarism. In fact, organotherapy is principally useful in chronic disease, anyway, and to consider the matter as thoroughly as the subject deserves would keep us too long.

We now come to the second and perhaps the more important part of this paper—the relation of the glands of internal secretion to cancer and the possibilities of organotherapy in this condition. This is neither the place nor the time to discuss the physiological basis of cancer or to speculate upon the how or why of this disease. We may, however, enumerate several promising and quite thoroughly substantiated theories: (1) Cancer is a chronic intoxication; (2) its incidence evidences the lack of an element in the blood which permits cell proliferation at a point of particularly lowered

resistance; (3) it is essentially a disease of senescence or, as Hastings Gilford has termed it, "cell senilism."

Seven or eight years ago many hopes were raised following the publication of the results of work done by Dr. John Beard of Edinburgh, and quite an impetus was given to the study of organotherapy in cancer because of the fact that trypsin was then brought forward in medical and, unfortunately, lay magazines as "worthy of immediate trial in the behalf of the many persons to whom it offers a possible chance of escape from an otherwise inexorable fate." Seemingly the attention of the public was drawn prematurely, for there has been no remarkable reduction in the mortality statistics nor do any of us here consider that pancreatic ferments are more than an incidental measure of relief in cancer.

It must be admitted, however, that Beard's work virtually inaugurated a more enthusiastic and searching consideration of organotherapy in cancer and while we have advanced many steps since 1906 we must not be satisfied yet. In the words of a recent writer: "We have survived too many hypotheses in regard to this elusive disease to accept further generalizations however plausible they may be at first inspection of the evidence; yet we are always glad to recognize every scintilla of a new suggestion which may furnish a welcome guide to progress."

With the foregoing in mind it may be well to collate a number of ideas which indicate a relationship between the incidence of cancer and ductless gland disorder, so that we may use them as a foundation for possible lines of treatment in this direction. They may also serve as a basis for explaining the not infrequent reports of the good results from organotherapy in cancer which are to be found in the literature.

We know that cellular activity is influenced by the hormones, or chemical messengers, that nutrition responds in a greater or lesser degree to their influence, and that it is possible to favor the reaction of the body against disease by the ingestion of certain organic extracts. The first question which naturally suggests itself is: Is not cancer more than a chronic disease such as the more benign metabolic disturbances previously referred to? Is it possible to influence by means of organotherapy an unquestionably organic condition when the action of the endocrine principles is supposed to be upon function rather than upon structure? Undoubtedly no form of internal medication at present known will destroy or remove the fundamental organic conditions pathognomonic of cancer, but it is entirely possible that the resistance of the sufferer from cancer may be increased to such a degree that other measures in common use may be backed up by an increase in the responsiveness of the cells and a general enhancement of nutrition.

Some individuals, for reasons at present only premised, present a special receptivity to the implantation and growth of cancer cells. Why this should be so and just how the cells become implanted is not for us to consider here, although it is a very fascinating subject and will, I believe, some day be thoroughly elucidated. I think it will be found to be much more intimately concerned with the internal secretions than is at present generally believed.

Clinically, the one essential symptom of cancer is waning cellular activity. Almost invariably nutrition is poor and with few exceptions cancer is limited to individuals past the prime of life, a fact which indicates there may be a direct connection between the activity of those organs of internal secretion whose work ceases at this period and whose action is no longer needed. Experimentally it seems to be proved that there is a basis for the idea that the susceptibility to the implantation of the cancer cells is in some way related to the gonads and evidence of this is to be found in the investigations of Sweet, Corson-White, and Saxon of Philadelphia, who found that when tumors were transplanted into animals (mice) which had previously been castrated the frequency of the establishment of the cancerous implant, as well as the rapidity of its proliferation, was considerably more noticeable in the animals that were thus rendered more susceptible.

If we admit that an important factor in all cancer cases is chronic cellular intoxication, then obviously a part of the treatment consists in favoring the activity of the known detoxicating organs as well as removing all nidi of further trouble, chiefly, of course, in the alimentary canal. The thyro-parathyroid apparatus is intimately concerned in the destruction of toxins and it is not remarkable to find a number of references in the literature to the fact that in cancer subjects the thyroid is usually found to be more or less atrophied. Parenthetically, it may be remarked that thyroid hypofunction is very much more common than until recently has been believed, and it is entirely possible for the thyroid cells to be seemingly normal from a pathological standpoint and yet be failing very materially in the production of those substances which are responsible for the carrying out of the "altruistic work" of this gland. Of course there has been considerable opposition to any theory which definitely connected the thyroid with this disease for thyroid therapy will be found to have practically no influence at all upon cancer.

The association of intestinal fermentation, however, has long been observed in cancerous individuals and has even formed the basis of several theories as to its etiology. One of the well known manifestations of the cancerous cachexia is achlorhydria and the resulting digestive disabilities. For this reason I recommend as a reasonable organo-

therapeutic procedure in all cases of cancer the attempt to re-establish the activities of the digestive glands by the administration of secretin. This alimentary hormone, secured from the duodenal walls, is a physiological means of stimulating the functionally inactive glands of the pancreas, liver, and intestines. Another sound reason for this particular adjunct measure lies in the fact that the absence of HCl from the stomach removes the normal stimulus to secretin production, since prosecretin is converted into secretin and released from the duodenal walls only by contact with the acid chyme, which is practically always absent in cancer. Further, since the action of secretin is not limited to the digestive glands themselves, but also distinctly favors the production of secretin in the duodenum itself, its value should be doubly evident, and the advantages accruing from the enhanced digestion resulting from this procedure reduce the toxemia normally present in cancer and at least must be considered one factor, even though a small one, in the treatment of this disease.

The second of the postulates previously set forth suggests the absence from the body of a certain element, or series of elements. Just what is missing from the blood of the cancerous is not yet well known, although the work of Abderhalden and those his research has stimulated indicates a definite series of substances may be concerned in this matter. Weiss has gone so far as to show that

serodiagnostic tests demonstrate an opposite behavior on the part of the serum from cancer patients and normal serum, and that this definite lack permits cancer cells to proliferate, principally at parts exposed to mechanical stress or irritation. He even suggests it may be possible to isolate from normal serum the element in question, the lack of which permits malignant proliferation, and utilize this in the prophylaxis and treatment of cancer. However near this may be to the truth, it will obviously be an extremely difficult matter to make practical use of it, at least to any considerable extent, and we must look still further for encouragement. This missing element, to my mind, will likely be found to be produced by the endocrine system, and, since the evidence already deduced indicates that this is not an unreasonable premise, the therapeutic possibilities are materially increased, for we now know with considerable certainty that when there is a functional hypoendocrinism or reduction in activity or service to the body of certain of the internal secretory organs, not only can the missing substances be replaced, but the semi-active organs may be stimulated by certain organic extracts in accordance with Hallion's law of homostimulation: "Extracts of an organ exert on the same organs an exciting influence which lasts for a longer or shorter time. When the organ is insufficient it is conceivable that this influence augments its action and, when it is in-

jured, that it favors its restoration." Resulting from these and similar premises quite a number of attempts have been made to use organic extracts alone and in various combinations as a part of the treatment of cancer. While we have not yet found an ideal remedy, it seems certain that organic extracts do produce beneficial results of varying degree.

The spleen and thymus offer probably greater possibilities than many of the other glands, although I think that eventually the optimum preparation will be a pluriglandular extract containing these and other synergists. The therapeutic administration of spleen extract increases nutrition, of that I am quite convinced, and those who have followed the work of Bayle of Cannes in the use of spleen emulsions and extracts in the treatment of tuberculosis cannot but be convinced that there is good reason for his success. His report to the International Congress on Tuberculosis in Rome is extremely interesting. I have personally had a number of communications from this gentleman, as we have for some years been mutually interested in each other's work, and when the war started he was engaged in translating my book into French.

Bayle's explanation of the sometimes remarkable influence of spleen extract is based upon what he calls its "colloidogenic" action. His theory is this: The blood contains the mineral elements in two forms—(1) Those in a colloid state suitable

for cellular appropriation, and thus not suited for elimination by the kidneys, and (2) the mineral cellular wastes, which are dissolved in the plasma, and are destined to be eliminated. If the colloid elements lose their colloidal form they are promptly eliminated and a condition of demineralization obtains. The capacity to maintain the mineral salts in a colloidal state is evidently of considerable importance, and, according to Bayle, seems to belong to the spleen. Bayle states that he has always found that splenic opotherapy quickly reduces an excessive elimination of phosphates in the urine. All of this deserves to be tested experimentally and clinically.

Now, there is undoubtedly a condition of mineral starvation in all cachectic states, including that of cancer. This has been frequently mentioned in the literature, and is referred to in an editorial in the Journal of the American Medical Association in the following words: "This is, however, little less than the metabolic story of partial inanition which attends the cachectic states which accompany so many chronic diseases. The demineralization, that is, the gradual and undue loss of all inorganic elements from the organism, is likewise not to be regarded as characteristic of cancer alone." This is admitted, for one of the principal manifestations of tuberculosis is this very condition, which explains Bayle's suggestions and his successful application of splenic-opotherapy in the

treatment of tuberculosis. There is no reason, however, why the same fundamentals should not be as applicable in the therapy of cancer as of tuberculosis, and this may be an explanation of the good results occasionally reported from the use of spleen extract.

Another gland frequently classed with the spleen, or at least with the lymphatic glands, is the thymus and more clinical work seems to have been done with thymus extract in cancer than with any other single extract. In 1907 Dwyer reported a number of cases that were benefited by this form of treatment and the more recent experimental researches of Rodenburg, Bullock, and Johnson, of this city, seem to prove that the products of the ductless glands are destined to play a certain role in our fight against cancer, and their recommendations include the use of thyroid, thymus, and other extracts as part of the treatment.

Some very interesting work in the study of cancer has been done by Dr. Seelye W. Little of Rochester, N. Y., and as a result of this he outlines certain facts which he has inferred from quite a number of clinical experiences. In the main his contention is that the reproduction of the reverted cell types in cancer is caused by the relative hypofunction of certain of the ductless glands and that to produce a cancerous growth such hypofunction must be primarily in an internal secretory organ derived from the same blastodermic layer as are

the cells from which the cancer originates. As a result of this he suggests that mammary carcinoma implies hypofunction of some endocrine organ derived from the ectoderm, since the breast is ectodermic in origin. He has also shown that the metabolism of sugar and calcium are intimately connected with the disordered nutrition of cancer and connects this in a very convincing manner with those glands which exert a vital relation to the metabolism of sugar or calcium or both.

Little's experiences are fascinatingly outlined in his papers published in the Boston Medical and Surgical Journal last year, to which the careful attention of every student of this subject should be drawn. His clinical findings warrant the use of several organic extracts, principally from the pituitary, parathyroid, adrenal cortex and the islands of Langerhans. In his most recent paper, in addition to emphasizing the value of sugar feeding in many cases of cancer, he has settled down to three ductless gland extracts as essential, one each for ectodermic, mesodermic, and endodermic cancer. For the first he uses total pituitary extract; for the second an extract of the adrenal cortex; and for the third an extract of the pancreas rich in the islands of Langerhans. All through his communications there is an underlying element of judicial research. He is not ultra enthusiastic and does not claim to have discovered a panacea for cancer. One cannot but believe from the clinical results of his

work that he is on the right track and that the conclusions which may be drawn from some of the facts gathered together here this evening warrant the continued investigation by a much larger number of students of the subject, not only of the relations of the ductless glands to the incidence of cancer, but the prophylactic and direct treatment thereof by organotherapy.

The third essential concerns the relation of the incidence of cancer to senility. We cannot deny that senility is the result of changes in certain of the internal secretory organs and that by far the greatest cancer incidence will be found in individuals well past the apex of vital activities. Just as fungus growths are usually found on decaying trees, so the similar cancerous manifestations are evidences of senile decay. Dr. Hastings Gilford of Reading, England, writes occasionally on the various subjects connected with senility and the ductless glands, and while at times he delves deeper than I am able to fathom, he is undoubtedly correct in his theories regarding cancer, that it is essentially a form of cell senility. He says that "certain somatic cells become dead while the tissue around them is still in a state of comparative youth. They express their senility by returning to a more embryonic form and as they do so they increase in number, the faculty of proliferation being one of the manifestations of regression." These senile changes may be presumed to be connected with

disturbances in the hormone balance.

This brings us to the consideration of another important phase of this subject—whether it is possible to use these organic extracts as prophylactic agents. I think it may be, but it is very difficult to know how and when to begin, for usually patients suffering with cancer do not give us the opportunity of investigating their trouble until the disease is well established.

Dr. Robert Bell of London has written telling "How to Destroy the Cancer Scourge," and aims to do this by restoring the vital energies of the whole cellular structure by what he considers to be a suitable diet. Unfortunately, however, recourse to this diet does not seem to have become the fashion yet, and the scourge is not being destroyed. The cancerous individuals are always run down; they are in a state of receptivity to disease and are obviously sufferers from pluriglandular insufficiency. If this subject is more carefully studied—it is remarkable how extended are its ramifications and how practical are the resulting clinical deductions—the reasonableness of this position may be clear to you. In other words, suitable combinations of glandular substances may be given empirically where a more or less obvious deficiency is presumed.

## XV

### SOME REMARKS ON THE TREATMENT OF HYPERTHYROIDISM

THE editorial invitation extended in a recent issue of Clinical Medicine, to "throw more light on this subject" of hyperthyroidism, prompts the following remarks, which, it is hoped, may be of interest because of the numerous and widely differing measures suggested in current medical literature for the treatment of thyrotoxicosis, or hyperthyroidism.

To my mind, there are three important things to accomplish or to attempt to accomplish in the treatment of this troublesome condition; namely:

First, the control of the toxemia, and especially of its serious cardiac manifestations;

Second, the removal of the sundry and widely differing causes of the thyroid irritability; and

Lastly, the re-establishment of the deranged metabolism and the "building up" of the badly disorganized cell nutrition.

The immediate treatment of cases of hyperthyroidism, in my estimation, centers on the control of the heart's action; and this is accomplished most satisfactorily by placing the patient at absolute rest in bed, in a quiet room away from the numerous

worries and noises of the home. Cold applications over the region of the heart and of the thyroid gland exert some beneficial effect.

By far the most important remedy, in my experience, is the extract of the posterior lobe of the pituitary, which may be given, by intramuscular injection, daily in doses of a 1-2 to 1 mil (Cc.) of the usual standard solution. I have had occasion to use numerous sedative remedies, and none seemed to exert so particularly beneficial an effect as this organo-therapeutic wonderworker.

The usual effect of these injections is, the reduction of the pulse rate by from 30 to 70 beats a minute, while, by its remarkable influence upon so many functions, it also favors the intestinal activities as well as increasing diuresis. According to Pal, the principle of the posterior pituitary lobe appears actually to exert a well-defined antagonistic action upon the unruly thyroid gland. Whether the pituitary gland contains a principle that exerts an effect opposite to that of the thyroid gland (an antihormone), has not been established; still, I am convinced that, clinically at least, pituitary therapy is as profitable an advance in the treatment of hyperthyroidism as is any measure suggested in the past and deserves much wider application and study in practice. This matter will be referred to again shortly.

Since it is imperative to accomplish some immediate and tangible results by the symptomatic

treatment of the patient and particularly the heart's action, it is in order carefully to investigate every possible source of toxemia and to antagonize it to the best of our ability. Undoubtedly the most fertile field for toxemia is the intestinal canal, and my routine treatment in such cases, instead of resorting to purging-treatment by mouth (toxins released by vigorous purging exert a very unfortunate effect upon the symptoms and have, indeed, led to the dismissal of the physician because of the severe reaction following the well-meant and none the less much-needed treatment), is to prescribe a series of oil enemata administered on three successive evenings. These enemata should consist of 5 or 6 ounces of any convenient oil (cotton-seed, olive, almond), warmed to the body-temperature and injected with an ordinary bulb-syringe, being made, by position and gravity, to reach the farthest end of the large intestine. This injection is to be retained all night. It has been found that its repetition on the second and third nights may bring away still more impacted material that was not loosened by the first one.

Parenthetically I will mention that many subjects of hyperthyroidism have an associated condition that might properly be called mild mucous colitis, and I am beginning to believe that there subsists a distinct relation between this disease and serious endocrine disturbances. At all events, where intestinal irritability is discovered and the patient

has been passing more or less mucus, 1 ounce of the pint of oil may be replaced by 1 ounce of ichthyol (or, as I have been using more recently, ichthyonat), which suffices to soothe the intestinal wall while it also exerts a certain degree of anti-septic action.

If laxatives are prescribed, they must be of the gentlest-acting nature. Cathartic pills, pills of aloin, belladonna and strychnine, and active alkaloid-containing stimulants are not advisable, because of their vigorous action and also because of a frequently undesirable simultaneous effect upon the heart.

The next procedure consists in neutralizing the alimentary toxemia as far as possible and, at the same time, since it has been demonstrated beyond question that the majority of the alimentary wastes are acid in reaction, alkaline treatment is in order. It is my custom to direct the patient to drink during the twenty-four hours at least 3 pints of water in which from 60 to 100 grains of sodium bicarbonate is dissolved, but laying strong emphasis on the necessity for not taking any of the alkaline water within one hour before or three hours after meals. If a 2-quart Mason jar is filled three-fourths full with water and the soda is dissolved in it, not only does it facilitate the measurement, but the sight of it, in a conspicuous place, serves as a reminder, toward the close of the day, whenever the patient has not been drinking the amount ordered.

Furthermore, the fact that the water contains a prescribed remedy and the reason for its administration has been made clear, prompts the patient to overcome any difficulty he may experience in disposing of this quantity (unfortunately, it is not the rule, in these cases at least, to drink sufficient water), for he realizes that it is not merely the drinking of water but the following out of a part of the doctor's course of treatment. In addition to the foregoing, I frequently have prescribed the combined sulphocarbolates as a means of keeping the intestine as nearly aseptic as possible. The dose should be at least 30 grains a day; however, it seems poor policy to waste good medicine of this character by not first giving the intestine a thorough cleaning out. In other words, the sulphocarbolate tablets must not be prescribed until the fourth day of treatment.

Occasionally in severe cases there is a more or less intractable diarrhea, and for the control of this feature I have been using protan with success.

The intestine by no means is the only source of toxic substances that irritate the thyroid gland. Thus, it has been found quite frequently that pyorrhœa is an accompanying disturbance in these cases, so that this condition must be treated locally, and thoroughly. The use of iodoglycerol as a local antiseptic and as an indicator of "dirt" on the teeth (which latter must be removed mechanically) is of great advantage. Various antiseptic dentifrices

and mouth-washes profitably may be recommended, while I have seen injections of emetine bring about very favorable effects, not merely upon the amebiasis, but also upon the thryoid gland and its functioning.

Other common sources of irritation of the thyroid gland are: diseased tonsils and infected nasal sinuses (frontal, ethmoid or sphenoid), pelvic infections, and, incidentally, local trouble in the angles of the intestine, the gall-bladder, and elsewhere.

The doctrine of focal infection was never more applicable and practically useful than in the "diagnostic treatment" of thyroid disorders, and many a failure satisfactorily to control dysthyroidism has been owing, not so much to inappropriate treatment, as to the fact that some hidden source of toxemia was overlooked.

Before leaving the sources of thyroid irritation, emphasis must be laid on still one other very important cause of functional thyroid troubles. We are now convinced, by the writings of Elliott (London), Sergent (Paris), and Cannon (Boston), that the emotions exert a specific effect upon the chemistry of the body, through the faculty of the adrenal glands to respond to emotional stimuli. Fear, rage, pain, and even worry, all excite the chromaffin system and through this effect cause sensitization or irritation of the entire sympathetic mechanism.

A case of exophthalmic goiter is on record which

developed suddenly, as from a clear sky, immediately following the mental strain imposed by the San Francisco earthquake. I have seen a number of cases recently in which the emotional element was unfortunately prominent. One case in particular originated from the shock of an insignificant fall of a foot or two. Another was aggravated by family troubles, while a third one, progressing nicely under my routine treatment, was set back abruptly and the pulse bounded up 40 beats a minute because of the excitement accompanying a sudden sickness of another member of the family.

Unfortunately, the control of the mental and psychic influences is most difficult; nevertheless, it is of highest importance to attempt as best one may the removal of the sources of psychic irritation—fear and worry, and, be it remarked, much “company” and exciting reading.

Practically all subjects of hyperthyroidism are poorly nourished, despite the fact that they may be hearty eaters and their digestion may seem to be perfectly normal. The reason for this is, of course, that the thyroid gland controls cell nutrition and the excessive stimuli coming from this gland, as the result of its disordered function, cause the foods to be burnt up too rapidly; malnutrition and even emaciation, hence, being the rule.

For this reason, the dietary must be generous and fattening. In addition to three liberal meals containing as few purin-bearing articles as possible,

I am in the habit of prescribing buttermilk prepared with a reliable culture of the bulgaric bacillus and to be drank at least twice a day, conveniently fitted in between the meals; and crackers with the buttermilk, if the patient cares for them. I am also partial to ice-cream as a daily adjuvant to the dietary, not merely because of the gustatory pleasure it affords, but because of its high caloric value.

Another article of the diet suggested—one possibly not possessed of any well-defined nourishing value, but which is of undoubted service, not alone in this disease, but in many nutritional disorders, is a rich vegetable consomme prepared by cooking together various and differing combinations of vegetables, especially the green stuffs. In these, I include: spinach, beet tops, turnip tops, celery (including the leaves), celeriac, asparagus (not in every case, because of the renal stimulant present), tomatoes, fresh young peas (with pods included), stringbeans, turnips, potatoes, in fact, almost any vegetable, boiling them in sufficient water for a long enough time completely to extract the saline elements, so that they may serve as an efficient nutrient instead of being thrown away, as is the rule in our present wretched cookery. Needless to repeat here that these vegetable salts are of real value in many disorders of metabolism, and, surely, it is correct to put hyperthyroidism in this category. Incidentally, the cook can modify the flavor and color of the consomme and change its concen-

tration at will; the form of serving may vary from a hot cup to jelly (made with pure gelatin); it may be given iced or frozen; also, it makes a very palatable dietetic adjuvant in many conditions.

Not infrequently the oral administration of pancreaticin may prove of distinct advantage, and I sometimes think that it has a dual action, in not merely increasing the digestion and, hence, favoring the assimilation of more much-needed food, but also acting upon the sympatheticotonic condition characteristic of this malady.

A word of explanation may here be in order. Toxemia having its origin in the thyroid gland or from any other cause, including the emotional stimuli referred to, gives rise to hyperadrenia; in fact, hyperthyroidism nearly always is accompanied by hyperadrenia, as may be quickly demonstrated by the application of Loewi's instillation test (putting one drop of adrenalin solution into the conjunctival sac and observing its influence upon pupillary action).\* The dry mouth, the tremor, and some

\*Quoting from W. M. Barton's excellent little "Manual of Vital Function Testing Methods and their Interpretation" (Boston, Richard G. Badger): "In 1908 Loewi made the observation that after removal of the pancreas in certain animals, the installation of adrenalin into the eye will cause dilatation of the pupil. Loewi attributed the mydriasis to increased excitability of the sympathetic system brought about by the removal of the inhibitory effect of the pancreatic internal secretion."

This has been used successfully in diabetes mellitus, but it will also be positive in Graves' disease due to the increased sympatheticotonus. Hence it is valuable in both these conditions, the reaction in the former being due to a deficiency brought about by the lack of the pancreatic hormone and in the latter to an excess of the chromaffin hormone (the mutual antagonist to the pancreatic hormone).

of the other nervous manifestations seem to me to be as much of adrenal as of thyroid origin. Now, it happens that the internal secretion of the pancreas exerts a decided antagonistic action upon that of chromaffin cells, and, in fact, it has by some been called the "pancreatic anti-hormone"; hence, any means of facilitating this function of the pancreas (in addition to its external secretory powers) is distinctly in order.

The administration of pancreatin not merely assists in digesting certain foodstuffs in the bowels, but, like all organotherapy measures, brings about a homostimulant action or, in other words, it favors the work of the pancreas, increasing the output of its chemical substances. Within the past year, several communications regarding the use of pancreatin in hyperthyroidism have appeared in print, and, as for myself, while I do not think of making it the main treatment, I consider that 15 to 30 grains or more per day, given after meals, certainly makes a useful adjuvant.

All the above seems to be of practical value, while I have purposely refrained from commenting upon the fairly well-known drug-treatment and the consideration of the need for surgery and Watson's excellent quinine-urea injection-method, all of which are the subjects of recent communications.

I cannot refrain, however, from recommending the method of treatment suggested last year by Dr. George Richter, of St. Louis, which consists in the

daily administering from 15 to 30 grains of the desiccated anterior lobe of the pituitary body. I have adopted this treatment in the case of 11 patients, some of them ambulatory and others resting in bed, and am convinced that there is brought about a valuable sedative action that is of distinct advantage, and I am hoping to be able some day to say definitely that this endocrine organ is the remedy for hyperthyroidism. At present, I can recommend it as a very useful adjunct to the other treatment above outlined, which has become a routine in my hands because of its effectiveness and reasonableness.

## XVI

### THE MAMMA AS AN INTERNAL SECRETORY ORGAN: MAMMARY THERAPEUTICS

IT is surprising how many of the glandular structures of the body whose secretory activities are so well known are beginning to be classed as having an additional and equally important function, i. e., that of internal secretion. It now seems beyond question that in addition to the pancreas, liver and gonads, the mammary glands also must be classed among the organs with a dual function, that of the production of both internal and external secretions. Incidentally, there seems to be some basis for the belief that the parotid is another of the glands with ducts which must be considered as having an internal secretion as well as an external secretion.

The fundamentals which serve as the basis of this paper may be summarized in the following postulates: (1) The mammae, in addition to their galactogenic function, produce an internal secretion, are themselves subject to hormone influences, and hence must be considered as part of the endocrine system. (2) Suitably prepared extracts of the mammary parenchyma contain a principle (presumably a hormone) which exerts a definite physi-

ologic action, and hence have inherent possibilities of therapeutic utility.

There are quite a number of reports of experiments made in different parts of the world which give abundant evidence of the truth of the first postulate, a limited number of which will be referred to briefly here. It is convenient first to consider the hormone control of the mamma and later to mention its hormone influence upon other organs and functions.

In 1906, in the Institute of Physiology, University College, London, Starling\* and his associate, Miss Lane-Claypon, demonstrated that the fetus is the seat of the production of a hormone which, passing through the placental circulation to the mother, brings about a specific stimulation of the mammary glands, first to enlarge and later to perform their milk-producing function. This substance seems to be of a definite chemical nature, and may even be obtained from dried embryo substance, from which it is extracted in a manner somewhat similar to the production of secretin from the mucosa of the duodenal walls.

One of the most remarkable of all their experiments was the establishment of lactation in virgin

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\*A pioneer in the study of the hormones, the discoverer of the "original hormone" secretin, and the originator of the term "hormone" (Gr., I arouse, excite or set in motion). Quite a full consideration of the history and importance of Starling's work with secretin, as well as of the importance of the discovery, production and action of hormones and the fundamental principles of hormone therapy will be found in my recent work, "Practical Hormone Therapy."

rabbits by the injection of these extracts. Several other investigators since have confirmed this work, and, in addition, have shown that fetal extracts from one animal will be active in bringing about this definite physiologic action in animals of a different species. So far as I am aware, no use has been made of this in medicine, for obvious reasons. Be that as it may, this was an important revelation, although it was by no means the original work which showed that the mammary gland was influenced by the chemical messengers. The experiments of Ribbert, made in the late nineties, seem to be the first in this line, and while they did not quite reveal the character of the stimuli, they undoubtedly proved that the development of the mammary gland was not solely under the nervous control. Ribbert and his associates transplanted a portion of the mamma from a virgin rabbit into a pregnant animal, and in due time the graft developed and actually secreted milk.

The fetal hormone or, as it was originally termed, the "mamma hormone,"\* is not the only chemical

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\*The term "mamma hormone" is fortunately becoming rare, since, as will be seen later, this term properly designates the hormone produced in the mammae—not the hormone which activates them. Incidentally, it will be remembered by those acquainted with the remarkable results of the work done with secretin, that it was originally called "pancreatic secretin," not because it is produced by the pancreas, but because it activates it. It is now called "duodenal secretin," because it is produced in the duodenal walls, though, of course, it still remains the principal activator of the pancreatic glands. The later nomenclature makes it possible to differentiate between secretins from varying sources, as, for instance, the gastric or pyloric mucosa.

messenger concerned in the control of the mammae, for it is evident that other hormone factors are concerned in the development and establishment of mammary activity. There is a very intimate relationship between the ovaries and the mammae, which has been demonstrated by Bouin and Ancel. These investigators found that by artificially rupturing the luteal follicles of the ovaries of rabbits, in addition to causing the discharge of the ovum there was produced a chemical substance—a hormone—which causes a marked histological change in the mammary gland, quite apart from the presence of the products of conception in the uterus (for the rabbit was not pregnant). In considering the reports of these remarkable experiments, an editorial writer in the Journal of the American Medical Association states that "these facts serve to lend new emphasis to the dependence of such physiologic response as mammary development on other than purely nervous relations. They add to the coming significance of hormone activities in the interdependence of various parts of the organism."

It is a well-known fact that experimental, as well as clinical, ovariectomy frequently is followed by retrogressive changes in the breasts and even by their disappearance, while experiments on animals have shown that under such circumstances an ovarian graft will bring about a re-establishment of the growth and activity of these organs. There

seems to be conclusive proof that the internal secretion of the ovary is a factor which controls or at least influences mammary activity.

The study of mammary development may be quickly broadened into a study of the hormone influences which control these organs, and a very complete consideration of this subject forms the These de Doctorate of Schil (1912). A resume of Schil's work will be found in my book, "Practical Hormone Therapy," and I can do no better than to include a part of it here:

Schil recognizes six stages in the evolution of the mammae: (1) The stage of development, divided into an organogenetic phase and a phase in which there is secretory activity (the lactation of the new-born). This secretory phase is dependent upon a hormone passing from mother to fetus through the placenta. This same hormone activates mammary secretion in the mother. (2) The pre-pubertal stage, which lasts until puberty (or the first rut in animals), during which the glands are functionally inactive. (3) The stage of puberty, characterized by a considerable increase in the glandular parenchyma. This growth is dependent upon the exciting influence (by means of a hormone) of the mature Graafian follicles in animals, in which non-spontaneous ovulation is produced artificially, and in the case of spontaneous ovulation, to the follicles and corpora lutea, which develop from these follicles after dehiscence. (4) The

gravid stage, which is divided into two phases: a, Growth, especially evident during the early part of gestation, as a result of which the glands attain their complete development; and, b, a so-called "phase glandulaire gravidique," which follows the completion of growth and is characterized by secretory activity, the product of which is known as the "colostrum." Each of these two phases is the result of hormone action, the first due to a kinetogenic hormone from the corpus luteum of pregnancy, and the second to a criticogenic hormone, which seems to come from a secretory portion of the placenta during the second part of gestation, or from a myometrial gland. (5) A post-partum stage, continuing during lactation until the glands are again in repose, and divided into two phases: a, Post-partum glandular activity, in which the milk is produced; and b, the phase of post-partum retrogression, in which galactogenesia ceases, and the parenchyma is slightly diminished. Of these two phases only the first is of interest, since the second is caused by the absence of stimuli. The milk, released during pregnancy by an endogenous stimulus, is maintained by an exogenous stimulus, the act of suction. (6) A senile stage, associated with involution, and corresponding to the period of cessation of genital activity.

There is, of course, further proof of the intimate relationship between the mammae and ovaries, as for example, the well established fact that the oper-

ation of spaying dairy cows at the time of giving their greatest flow of milk has an influence upon the lacteal period. In a personal communication from the Bureau of Animal Industry the following appears: "It is a well established fact that in spayed dairy cows the period of lactation is prolonged."

Additional emphasis is lent by the fact that the function of ovulation is retarded and sometimes entirely stopped during prolonged lactation, presumably because in the stage of mammary activity the increased elaboration of the internal secretion antagonizes ovarian activity in a greater or less degree. It is well known that pregnant cows as a rule show a tendency to lessen the supply of their milk after conception takes place.

In a conversation on this subject the other day, it was stated that quite frequently women with large mammary development menstruate scantily, while those with small breasts not infrequently are subject to menorrhagia. This is by no means always the case, but it points at least to an antagonism between the mammae and the ovaries.

As still further incontrovertible evidence of the hormone control of galactogenesis I will cite the remarkable experience of the famous Blazek twins. It may be remembered that this pair of pyopagous female twins matured and one of them married. In due time she became pregnant and was successfully confined and after delivery the secretion of

milk also took place in the non-puerperal sister. In other words, both were able to nurse the infant, and obviously the influences which stimulated mammary activity in the unmarried sister were of a hormone nature.

Most of these facts, it is true, indicate that the mammae are subject to hormone influences—i. e., are controlled in part by an internal secretion of the ovary, or other glands; but if the second postulate is considered, satisfactory proof of the internal secretory activity of the mammae will be forthcoming, for, as will shortly be seen, the antagonistic relation between the mammae and the ovaries is made good use of as the basis of certain therapeutic procedures.

A consideration of several of the numerous references to the use of extracts of the parenchyma of mammary glands as a therapeutic agent seems to show conclusively that they possess a decided therapeutic influence and at the same time emphasizes the importance of what must still be called a much neglected field of therapeutics. As a matter of fact I am sure that "hormone therapy," as I like to call it, is neither studied nor practiced as much as it deserves; and those who will take the time to investigate the scientific use of organo-therapeutic extracts will quickly find that the astonishing results accredited to thyroid, adrenal or pituitary medication are by no means limited to these few; but that a vast territory will be opened

up in which will be found many proved and, later, more as yet unproved, means which will facilitate the solution of many a therapeutic puzzle.

Mammary extract is produced from the carefully dissected parenchyma of the udders of cows, goats or ewes, and is prepared with the precautions customary in the manufacture of effective organo-therapeutic extracts. It is obtainable in dry form or in solution (in ampules). Injections of the latter seem to be somewhat painful and, so far as I can see, have no special advantage over the powder or tablets given by mouth, as in many cases the results are just as evident following treatment by the internal as by the hypodermic or intramuscular method, tending to prove that whatever the principle may be that is the cause of the therapeutic activity of this extract, it is not destroyed when passing through the stomach.

As we have already seen, there is a decided antagonism between the mammae and the ovaries, and this fact is the basis for the principal use of mammary extract. It is used to overcome the results of excessive ovarian activity. Among the conditions, which have been classed under this head are menorrhagia with increased uterine congestion, uterine hypertrophy and fibroid degeneration, as well as certain conditions in which there is an increased degree of ovarian activity. The chief every-day indications for mammary therapy are functional uterine hemorrhages and fibroids.

A number of investigators have used this method to produce uterine depletion and to control hemorrhages shown to be due to functional causes as distinguished from those of organic origin, such as the presence of foreign bodies in the uterus, polypi, placental remains, cancer, etc. Clearly medicinal therapy is not likely to be very effective in such conditions as these latter, where the removal of the foreign body or growth is the most reasonable procedure. However, mammary extract has been used in the post-operative treatment of such cases, especially when there has been a tendency to protracted oozing.

Pochon has used mammary substance and recommends it for its decided anti-hemorrhagic influence (however, it is not a styptic by any means) and calls attention to the fact that while mammary extract tends to cause uterine depletion, ovarian extracts have an entirely opposite tendency, causing an increased uterine blood supply.

Luncz, in his interesting monograph, has gathered a number of reports of benign cases in which mammary opotherapy caused an entire cessation of uterine hemorrhage in persons of widely varying age.

Other writers have gone further, among them Forgue and Massabuan, who besides demonstrating clinically the anti-hemorrhagic action of this preparation, have shown experimentally that at the menopause there frequently is an obvious in-

crease in the corpora lutea with hypertrophy of these cells. They presume that the hemorrhages so common at this time may be due to two causes: Temporary increased production of the luteal hormone, and an associated decrease in the production of its antagonist—the mammary hormone—resulting, of course, from the usual retrogressive changes expected in the mammae at this period. This harmonizes entirely with the facts previously collated here, and is further evidence of the soundness of the position of this form of treatment in such cases.

There are numerous reports showing the anti-hemorrhagic influence of mammary substance. I have personally prescribed and recommended it in a number of cases with good results. Battuaud indicates that this form of medication has proved valuable in the control of menorrhagia in young girls, just as it has been found serviceable in metrorrhagia of the climacteric. Congestive conditions of the ovary resulting from inflammation of the adnexa and other causes may be reduced in this manner, although, of course, the influence is more mechanical—i. e., decongestion is brought about in a chemical way and there is no particular action on the infective process. In other words, mammary extract is a valuable adjunct to the specific anti-infection treatment, which is now generally recognized to be the bacterin method.

Dalche, Jayle, Pozzi and other French gynecolo-

gists are convinced of the efficacy of this method, while virtually all the references to mammary therapy in American medical literature are quite a number of years old, the chief papers being those of Pryor, Crouse and Shober.

The original application of mammary therapy seems to have been made by Robert Bell, of Glasgow, in 1896, and his initial experiences were in the treatment of uterine fibroids. He reported before the British Gynecological Society four cases, two of which were suffering from fibroids, the first in a woman of forty-eight, the large fibrous tumor being reduced 75 per cent. after four months' treatment, the menstrual troubles having in the meantime completely disappeared. In the second case a smaller fibroma was much reduced in size after three months' treatment, the hemorrhage having been stopped and the anemia controlled.

In the last 18 years there have been, perhaps, 180 cases reported in the literature, the majority of them in Russia, although quite a number will be found in the French journals. Feodoroff, Professor in the University at Petrograd, has made several communications on this subject and in his most recent statistical report refers to a series of 43 women treated for fibroids, in 25 of whom the uterus had attained the approximate size of the gravid uterus at two or three months, in 16 others the tumor being larger and corresponding to the gravid uterus at four to six months, while in two of them the

tumor extended beyond the umbilicus. One-third of all these cases was completely cured; in 53 per cent. there was a decided reduction in the volume of the tumor; in over 80 per cent. the hemorrhage was completely stopped, and in 47 per cent. the pain commonly noted was relieved. In only 14 per cent. of this series was no result whatever secured. It is only fair to add that one-half of the complete cures were secured in the first series (those in whom the volume of the uterus corresponded to the pregnant uterus at two or three months) and that in the two extraordinarily large tumors no result was obtained. These figures, apart from the reports of several other writers, would almost seem to be convincing evidence of the value of mammary substance in therapeutics, for despite the fact that Feodoroff's name is strange in this country, he is a very well known gynecologist in Russia.

Another Russian investigator, Mekerttschiantz, is more enthusiastic in his praise of this method, and goes so far as to call mammary extract "the touchstone for all cases of uterine fibroids"; and rightly suggests that it be given a thorough trial for several months before operative measures are decided upon. (This, at least, is a fair presumption, for, in my opinion, the surgeon is not always justified in performing hysterectomy or pan-hysterectomy until every reasonable medical procedure has been thoroughly tried without avail.) He calls attention to the fact that uterine contractions

may be caused by this method, and also believes that the retrogressive changes that are brought about in interstitial fibroids are due to their transformation into subserous fibroids which later become pediculated and are either cast off or absorbed.

In all of his 50 or more cases, Mekerttschiantz secured benefit, the hemorrhage was controlled in all, the tumor reduced to a minimum in two-thirds, and a noticeable betterment in general health was remarked. It is interesting to note that in cases of fibroid complicated with pregnancy, mammary therapy exercises a maximum influence on the retrogression of the tumor, because the effect of the extract is amplified by the increased mammary activity resulting from the normal physiologic stimuli, as well as by the homostimulation\* which is also brought about.

Naturally in all organic diseases the possibilities for success in therapeutics are considerably less than in functional disorders, hence it must not be expected that the application of this method of treating fibroids is going to be nearly as effective as in the treatment of the less serious and more easily controlled functional disorders. In other words, functional menorrhagia responds to mammary therapy much more readily than do uterine

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\*“Homostimulation” is a term coined by Hallion of Paris to designate a uniform property of organo-therapeutic extracts which is summarized in what is now called “Hallion’s Law” (See page 3.)

fibroids; and in the treatment of the latter the hemorrhage and other symptoms likely will be influenced more and earlier than the tumor itself.

While the use of mammary extract in therapeutics has not yet reached the same unassailable position that has been attained by certain other glandular extracts, notably thyroid, pituitary and adrenal, it is none the less a useful procedure for the gynecologist and the general practitioner; and while the experiences outlined previously may not be always duplicated in their entirety, there can be no doubt that it is an effective method and that it deserves, like many other phases of practical hormone therapy, more fully outlined in my book of that name, to be raised from the obscurity in which it is at present involved.

It is not as difficult to secure effective mammary preparations as has been hinted by many with whom I have spoken or corresponded. In every country that I have visited I have been able to find useful preparations and no harm can come from referring to some of these. In England one can quickly secure Mamos (B., W. & Co.), Ovomammoid Comp. and the Russian product, Mamminum. In France there are at least 12 "extraits mammaires," those of Carrion, Choay and Chaix of Paris ranking among the best. In this country one can usually secure the products named above, as well as Mammary Substance (Armour & Co.) and Mammogen (G. W. Carnrick Co.), and most of my

more recent personal experiences have been limited to these latter.

Before closing, a few words may be said regarding dosage. It is usually advisable to give 5 or 6 grains t. i. d. Larger doses may be given, as much as 15 or 20 grains at a dose. (Attention is called to the fact that not every tablet contains the amount of actual substance that corresponds to the weight of the tablet, the amount varying with the products of different manufacturers.) It seems best to give mammary extract just before meals, for in occasional cases there is a slight tendency to digestive derangement following its use. In fact, rarely a case will be found in which it is necessary to discontinue the use of this preparation and to re-establish the dosage in very gradual steps, commencing with one or two grains a day and increasing as rapidly as is consistent with the circumstances.

Obviously in the treatment of conditions of long standing this method must be continued over a long period, and Battuaud in recommending 0.5 Gram ( $7\frac{1}{2}$  grains) of the active substance twice a day, suggests that when attempting to control hemorrhage between the periods the above dose should be continued daily and doubled during the hemorrhage. It has been suggested that mammary extract should not be given during the menses, but I have not found this so. After all, each patient is a law unto herself, and, as with many other therapeutic procedures, the best dose is "enough."

## XVII

### CONNECTING LINKS BETWEEN ENDO-CRINOLOGY AND OTO-RHINOLOGY

ON first thought the connection between the internal secretory organs and the ear, nose and throat is not particularly intimate and, perhaps, some of you have felt that the hour this evening might be ill-spent in listening to what I have to say. If so, I hope that you may be pleasantly disappointed, for I believe that the connection between these two branches of medicine is just as evident and as important as those well-defined links between other systems or organs of the body which have become better known as our knowledge of the hormones has increased.

For the sake of convenience I have divided my remarks into two parts, in the first of which I hope to show that a well-marked and fundamental relationship exists between certain of the glands of internal secretion and some of the disorders in your special field and vice versa; and in the second, briefly to consider several profitable phases of organotherapy which specialists such as yourselves may apply quite frequently.

Naturally the thyroid gland would be the first to engage our attention, for it is among the most

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An address read before the Eye, Ear, Nose and Throat Section, Los Angeles County Medical Association, May 1, 1916, and published in *The Laryngoscope* (St. Louis), August, 1916.

important of the hormone-bearing organs. The thyroid gland exerts the same influence upon the control of the metabolism in the cells of the structures constituting your province of medicine, as it does in the maintenance of cell nutrition and detoxication in any other part of the body. The great principle involved in the relation of thyroid insufficiency and the condition of cellular infiltration to which extended reference was made when I recently addressed the Los Angeles County Medical Society, is responsible for at least a part of the troubles which you are called upon to treat. Hertoghe himself mentions the frequency with which hypothyroidism is associated with noises in the ears and dizziness; and even Meniere's syndrome may result from this condition of infiltration which Hertoghe was the first to direct to the attention of the profession some twenty years ago.

I have encountered several cases of Eustachian infiltration with a degree of deafness which was at least partially due to this disorder, which cleared up when the quite generalized infiltration was recognized and its relation to thyroid inadequacy made the basis of the only proper treatment—suitable thyroid medication. It may not be out of place, then, if I should suggest that any of the intractable aural or nasal conditions in which a mucosal or more deep-seated infiltration might be present, should be a signal to you to search for other evidences of thyroid disorder. In case any of them

are discovered, and you will recall that they are not hard to identify, suitable organotherapy profitably may be made a part of your treatment. I am not saying that thyroid extract is a panacea for intractable nose and throat disorders or that it is the rational remedy for noises in the ears or deafness. I merely suggest that if any of these symptoms serves to direct your attention to an obscure thyroid trouble and you verify it by discovering other symptoms usually expected in this quite common disorder, it is rational therapeutics and profitable therapeutics, too, to exhibit thyroid; and the results will be sufficiently good in some cases to make up for the failures in others and at the same time to convert one to the importance of the diagnostic and therapeutic value of this suggestion.

It should not be necessary to remind you that adenoids are almost invariably found in hypothyroid children, so much so that it is now believed that this relation is not merely incidental, but that the thyroid dyscrasia may have some causative influence in the production of the abnormal growths. This being the case, it seems to be proper when studying adenoid children to look carefully for other evidences of thyroid insufficiency and, when they are found, to treat them simultaneously with the adenoids. With the risk of causing some slight offense by attempting to discuss a subject with which I am not very familiar, I will venture the statement that it is not good practice to treat an

adenoid case by the mere physical removal of the offending tissue, while the results of its presence, as well as the possible causative factors, still remain more or less definitely present. While adenectomy undoubtedly gives Nature a better chance to reassert herself, which she practically always makes the best use of, I believe that suitable organo-therapeutic and other measures will give her a still better chance if an insidious thyroid dyscrasia happens to be present.

We shall not have time to enter into a study of the broad subject of the ductless glandular disorders in that large class of cases which McCready, of Pittsburgh, chooses to call "children requiring special attention"; but it must be admitted that the first one to have an opportunity to investigate such cases is the oto-rhinologist, for the most marked and obvious disturbance calls for your service. Too often this service, usually operative, is all that is given and it is unfortunate. One should treat the whole child and not merely that disorder which obtrudes itself upon the parent, the teacher or the family physician.

I have directed your attention to a few of the conditions in the nose and throat which may be connected with hypothyroidism and before I get away from the thyroid gland, there is another phase of its study that has recently been emphasized. Naso-tonsillar infections are a common cause of thyroid dyscrasias. Those who have the

opportunity of studying many cases of goiter, both the so-called "simple" type and more especially the "exophthalmic" type, are beginning to realize that overlooked infections of the mouth, nose or tonsils are closely connected with the incidence of these thyroid disorders. Some reports of work done at the University of Wisconsin are very interesting. Evans, Middleton and Smith (1) examined the mouth, nose and tonsils of three hundred and sixty-two individuals with goiter. In no less than 22 per cent. of these there was a tonsillar endamebiasis, while a less marked but indubitable infection of other parts of the mouth and nose was present in a much larger number. The importance of this was proved by the treatment of a number of the cases in which there was a well-marked thyroid dyscrasia as well as a goiter, and out of twenty-three patients treated with emetine the dysthyroidism was favorably modified in eighteen cases.

So just as certain common symptoms that have been mentioned lead us to think of thyroid inadequacy as an etiologic factor in nose and throat disorders, so nose and throat disease may be a cause of well-marked thyroid troubles. The inter-relation is closer than has been imagined.

So far as the application of various phases of organotherapy in oto-rhinology is concerned, we have already mentioned some indications for thyroid therapy. Certainly it is worth applying in some of the old, difficult cases in which one can demon-

strate a more or less well-marked hypothyroidism. I need not tell you of the value of adrenalin, but perhaps not many of you have yet had recourse to some other organotherapy measures for the prevention of post-operative hemorrhage, especially in nose and throat surgery. The first is the intramuscular injection of pituitary solution as a means of preventing anticipated bleeding. Kahn, in one of your special journals, (2) states that he gives twelve minims of the standard solution of the posterior pituitary principle fifteen minutes before anesthesia is commenced prior to nose or throat surgery. The above dose is for children, fifteen minims or more may be given to adults. The coagulation time is reduced one-third to one-half and hemorrhage is greatly reduced, especially following turbinate operations. The cardio-stimulant influence should be also of much value.

The second anti-hemorrhagic remedy is prepared from brain tissue and has been named thromboplastin or kephalin and is used locally, being swabbed on the cut surface. It has been extensively used by certain clinicians and further information may be found in the writings of Hess (3) and Cronin. (4)

Another interesting and not very well studied phase of organotherapy is the use of lymphatic gland extract in adenoid children. I am not setting this forward as something so valuable that it should not be missed, rather I am relating an experience

which seems to hold within it something of ultimate clinical value. If the experiences which follow are worked out—and there are opportunities galore for such investigative work—it may be that some new and illuminating information may be had on the adenoid-tonsil question. Ashby, (5) of Liverpool, has suggested that the uniform enlargement of the tonsils and especially the growth of adenoid tissue in children at a fairly constant age may be a defensive act of the body, the increased tissue being an attempt on the part of Nature to supply some secretion or substance which is especially needed at this time when adenoid hypertrophy is most usual. The obvious deduction was that it might be possible to give this to the body just as the missing thyroid, ovarian or pituitary substance is of therapeutic efficacy in conditions of corresponding glandular insufficiency. So Ashby gave thirty children one gram of desiccated lymphatic gland each day for a number of weeks. There was obvious improvement, the hypertrophy was reduced, snoring ceased and noises during breathing disappeared. This is but a preliminary report and is surely deserving of further study, for the opportunities are so numerous and the possibilities quite considerable.

Your secretary reminded me to be sure to include something of interest to the ophthalmologists, and before closing, a word or two of possible interest to them may be added. Several important eye condi-

tions may be connected with ductless glandular disorder. One of them is not yet well differentiated for it is in the long category of troubles either due to or associated with hypothyroidism or, more probably, pluriglandular insufficiency. It consists of a fairly well defined asthenopia of obscure origin with a train of symptoms which is doubtless familiar to you with muscle weakness predominating. This is not an uncommon condition, and when the progressively decreasing powers of vision are not directly connected with a reasonable cause, and, for that matter, even when a cause is quite well defined, it is well to look for other symptoms such as those previously mentioned as being due to thyroid inadequacy. In such cases carefully graduated thyroid medication may be of quite considerable help.

I need but mention in passing the eye findings in exophthalmic goiter, a typical internal secretory dyscrasia, the treatment of which is usually out of the province of the ophthalmologist.

One of the most interesting ocular disorders is the bitemporal hemianopsia now known to be due to pituitary disease. Not uncommonly the ophthalmologist is the first to meet these cases, for the sudden or progressive visual disabilities naturally call for his aid first. It may be well to outline in all brevity the eye symptoms of well-marked pituitary disease. The enlarged gland in its sellar cup causes fairly uniform neighborhood symptoms—we are not now interested in which part of the

gland may be involved, nor what type of pathological changes may be present and what varying secretory dyscrasias result therefrom—and the chief among them affect the sight. The first of these is due to the direct pressure upon the optic chiasm with either primary optic atrophy (I think this term is incorrect as we may shortly see) or, more usually, bitemporal hemianopsia. This blindness varies in degree and rapidity of onset, but more often first affects the visual acuity for colors only, and later for form as well. Professor Cushing very kindly sent me last week a valuable monograph by himself and C. B. Walker, (6) in which the distortions of the visual field from brain tumors are interestingly considered. The conclusion of this study is worth reiterating: Detailed perimetry with small test objects of several sizes is advocated for patients with pituitary disease in order that stages of hemianopsia antecedent to those usually recognized may be detected.

The other eye symptoms are found in more marked cases, i. e., when the pituitary tumor extends beyond the sellar edges. In such cases there may be paralysis of both of the external recti with resulting internal strabismus due to pressure on the sixth cranial nerve, or by similar pressure on the third cranial nerve external strabismus may result. Still later the increased intracranial pressure will cause choked disc and ultimate total blindness. This condition and the so-called "primary optic

atrophy" (of pituitary origin) or descending atrophy does not necessarily mean an anatomical degeneration of the nerves, but according to Cushing (*loc. cit.*) it is very often only a "physiological block to the transmission of the visual impulses" which may be relieved speedily by decompression or other more serious surgical measures.

As in all other phases of medical endeavor the ramifications of the internal secretory threads are closely intertwined with every phase of physiological activity and as the skein is unravelled and our understanding of these interrelations becomes more comprehensive, there comes a better control of many conditions, the treatment of which has been beset previously with seemingly insurmountable difficulties. Enthusiasm in the study of the internal secretory organs and their disorders is not to be scorned, for it leads one into fields in which many of the flowers "born to blush unseen and waste their sweetness on the desert air" may be viewed, handled and appreciated as never before.

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## XVIII

### THE TREATMENT OF RICKETS

RICKETS is a nutritional disorder of children, a form of starvation, hence before it can be treated effectively we must know what factors are prominent in the production of the disturbed metabolism and what elements can be given acceptably to replace those that are deficient. From an experimental standpoint, rickets is now understood to be a result of endocrine disorder. It has been produced more easily and quickly by the removal or destruction of certain of the glands of internal secretion than by dietetic restriction. In fact, the dietetic element in the etiology of rickets seems to be losing a good share of the importance that was until recently attributed to it.

**Direct medication.** Five things need to be accomplished:

1. Replace the missing mineral element in the blood and bones—calcium. The best calcium salt is the phosphate, which is conveniently given in the U. S. P. syrup of calcium lactophosphate, two drams, three to six times a day.

2. Replace the missing vitamines, factors which are now being recognized as playing an important part in many nutritional disorders. In nursing chil-

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dren with serious malnutrition it is often noted that the mother is badly nourished, and suitable treatment will augment the value of her milk. In therapeutics this is accomplished by suitable dietetic regulation and by organotherapy.

3. Antagonize a tendency to acidosis which is invariably present in rhachitic children and is quite frequently overlooked. Sodium citrate is excellent for this purpose and, incidentally, when given with milk, it prevents the formation of large curds and thus favors digestion. When the urinary acidity is high, sodium bicarbonate may be given in small and frequent doses, well diluted and so timed as not to interfere with digestion; though the citrate has an almost equal neutralizing value.

4. Enhance the mineral content of the blood. In addition to the calcium salts we can advantageously give the salts secured from fresh vegetables. This is an extremely important part of the successful treatment of rickets, for these saline elements seem to be urgently needed by the system; and are easily prepared and assimilated. In France bone substance is used not uncommonly and perhaps there is some advantage in this organic form of calcium. Until recently preparations of bone (not bone marrow) were difficult to secure but Russell of New York has lately produced a preparation of green bone which should be as much better than the powdered bone as it is better than the ordinary mineral salts we usually prescribe.

5. Favor the restoration of the conditions which cause or aggravate the disturbed mineral metabolism. This is best accomplished by suitable organotherapy. Many times small doses of thyroid extract—one quarter to one half grain, three times a day—will influence the nutrition of the rachitic child in a most decided manner. Thymus extract has been recommended upon the theoretical ground that the thymus controls calcium metabolism and that rickets is possibly a manifestation of hypothyroidism, for a characteristic result of thymectomy in young animals is a typical rickets with marked softening and bending of the long bones, especially of the legs; and many autopsies of children dying with rickets show the thymus to be atrophied prematurely. Again, pituitary is occasionally recommended, while total adrenal substance has facilitated recovery after other measures had been tried with little or no benefit.

The stimulation of the endocrine glands is a matter of special importance, as unless this is done the calcium salts given simultaneously may be excreted and thus be useless, for it is certain that the fundamental factor in rickets is not so much a deficiency of calcium as an inability to fix and utilize it. This capacity is undoubtedly under the control of the ductless glands, those just mentioned being the most important.

Pluriglandular therapy is a useful even if empiric procedure in rickets. The following combination is

well worth trying:

Total adrenal substance.....	2 parts;
Desiccated thyroids .....	1 part;
Thymus gland .....	3 parts;
Excipient to make.....	10 parts.

Two or more grains of this mixture, depending upon the age of the child, may be given three times a day. The proportions may be varied, or pituitary substance (total) may replace one part of the excipient. A total of one and a half to two grains each of thyroid and adrenal, and ten grains of thymus may be given in twenty-four hours. Carpani (*Lancet*, June 19, 1915) recommends pluri-glandular therapy in rickets and gives powdered and dried gland substances in toto, in doses suitable to the age, in milk, for fifty days, omitting this for one week after the first month's treatment. He noticed rapid and striking improvement, especially early in the treatment, the benefit first noticed in the digestion, then in the nervous manifestations, and later in the blood and osseous system.

Another form of organotherapy which is quite generally used, is the administration of codliver oil alone or in various forms and combinations. The benefit is not due merely to the easily assimilated hydrocarbons, but also to the vitamines which are present and to a substance of a hormone nature which apparently aids in the metabolism of lime salts. Parenthetically it may be remarked that these substances are present in greater quantities in the cruder products, thus explaining the statements

of Leonard Williams and others to the effect that the cruder the oil, the better its therapeutic effects in many cases.

**Hygienic care.** Obviously the general care of rhachitic children should be as good as possible. Good hygiene favors all treatment, and usually children suffering with rickets have not had the home care they needed. The emunctories must be watched and regulated by the diet, by an occasional dose of castor oil, and, at the beginning of the treatment, by calomel in divided doses. The skin and circulation should be stimulated by daily cool bathing with friction. Sodium bicarbonate in the water (a heaping teaspoonful to each quart) is often an advantage, especially where the skin is chafed. Gentle massage with almond or olive oil is valuable. Sunshine, fresh air, suitable exercise, and regular rest are all important, especially the first two.

**Dietetic management.** Most rhachitic children have been poorly fed and the malnutrition is not confined to the bones. Digestion is poor and assimilation is reduced. Fresh milk, because of its richness in vitamines and "living salts," is by far the best food. Pasteurized milk is a poor substitute, prepared foods are usually unsatisfactory, and boiled milk is the worst food that could be selected. The value of sodium citrate has already been mentioned, and lime water is also useful in modifying the milk. Limits of space forbid a discussion of the necessary milk modification and its administra-

tion. Suffice it to say that the child must be fed with milk modified on the basis of its weight, not its age—at least until digestion is normal and the child is obviously improving. At this stage barley gruel, oatmeal gruel, corn flakes, and other “heavier” cereal foods may be added, and later potatoes (baked) and other foods as a tolerance for them is established.

Between meals plenty of fluid should be given, and it should be planned to carry in this as many of the assimilable, vegetable mineral salts as conveniently can be given. Small quantities of fruit juices, especially orange and prune, may be given two or more times a day. Often idiosyncrasies to these are found, hence the need for caution.

Another excellent dietetic adjuvant, I might better say therapeutic measure, is clear vegetable soup. Sometimes it may accomplish more than any of the direct remedies mentioned previously, since it contains Nature's minerals, which normally form the inorganic pabulum of the cells. The preparation of this soup is important, and, incidentally, it will be found a most valuable remedy in many metabolic dyscrasias in adults as well as children, including rheumatism, malnutrition, certain neurasthenic conditions, etc.

Spinach, potatoes (or well cleaned potato parings), carrots, turnips, fresh peas (with the pods), and, perhaps, small amounts of onions, are washed, cut up, and covered with two or three times their

volume of water. Raw wheat or bran may take the place of one or more of these vegetables, if desired. The exact ingredients or their relative amounts are not of such great moment. Simmer for three or more hours over a slow fire, or, better still, boil briskly for fifteen minutes and place in a fireless cooker for three to five hours. Strain without pressure. The remainder may be passed through a sieve and used as a basis for a palatable thick soup for the table. One to four ounces of this clear liquid may be given four times a day, with or between the feedings. Bran water may be used. It is prepared and given in approximately the same way.

The surgical care of deformed bones is a matter for the attention and care of the orthopedist. Braces may be helpful, osteoclasis is often advisable; but in any event the foregoing suggested outlines for the treatment must be associated with surgical care.

## XIX

### THE ORAL ADMINISTRATION OF ADRENALIN

THE active chemical entity prepared from the adrenal medulla is oxidized and destroyed very easily in the body. This accounts for the ephemeral effects which follow its administration as a remedy; and also the comparative rarity of the symptom complex of hyperadrenia. In vitro adrenalin is quickly destroyed by numerous reagents and it has also been shown that it loses its activity when in contact for a short time with the gastric juice. If adrenalin is given by mouth, and the stomach is evacuated ten minutes later, it is usually impossible to detect this substance. In the fasting stomach this disintegration is accomplished in almost the same time, though here the writer is by no means sure that this really means that the adrenalin is destroyed, for some of it is absorbed.

All these experiences have led to a quite natural impression that adrenalin was not effective when given by mouth, and that to obtain other than the well known results, it must be given by hypodermic or intravenous injection. There are not a few references in medical literature, including that of the manufacturers, which indicate that this idea is well grounded in the minds of the profession.

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For years I have been convinced by personal experiences that this opinion was misleading, and am confident that unquestioned therapeutic effects have followed the oral administration of adrenalin.

In a short communication to the editors of the New York Medical Journal (July 8, 1916, p. 94) Leland Boogher relates some interesting personal experiences following the use of fifteen minimis of adrenalin solution (presumably the standard one in 1,000 solution) in a tablespoonful of water by mouth for the relief of excruciating abdominal pain due to an abscess in the transverse colon. Boogher has since recommended this measure as an analgesic remedy for gallstone and renal colic, and "it gave splendid relief." This reference emphasizes what is probably an original application of this much used remedy; and credit for this should be given to Dr. George Richter, of St. Louis, who prescribed the treatment outlined above.

However, this experience is also corroborative evidence of a well established fact, still denied in many quarters, that adrenalin per os is both potent and useful. In American Medicine a number of items have been reported which substantiate this view. In the issue for April, 1915 (p. 253), there appears an article entitled "Giving Organotherapy Products by Mouth," by the writer, in which reference is made to the prevalent but mistaken notion as to the availability of many organo-therapeutic extracts when given per os. Reference was

there made to a statement to the effect that "these (organotherapytic) extracts, with the possible exception of thyroid, are destroyed in the stomach; hence it is useless to give them unless hypodermically." The writer then proceeded in the following terms: "This is not true, and the statement can be easily disproved. . . . Why, if organotherapytic remedies generally are destroyed by the digestive juices, should thyroid be the lone exception to the rule? Wherein does the active principle of the thyroid differ in its absorbability or destructibility from the hormones of the adrenals, pituitary, or gonads? The most conclusive and practical proof of the inaccuracy of such a position would be to have those who make such statements (or believe them) take, say, an ounce of one in 1,000 adrenalin chloride solution—it contains less than half a grain of the active principle—and note carefully if there is not a considerable modification of the circulatory equilibrium!"

Several of the statements as to the destructibility of adrenalin when given by mouth appear in the scientific publications of the American Medical Association, though, curiously enough, in the weekly department on Therapeutics in the Journal A. M. A. (October 16, 1915, p. 1366) there is a brief consideration of the emergency treatment of sudden cardiac failure from which the following statement is cited: "Epinephrine may be given in a dose of five drops on the tongue, which may be repeated in

half an hour if advisable. . . . All of the foregoing (including strychnine, hot coffee, camphor, etc.) are quick acting treatments." This casual statement is of unusual interest, since the use of epinephrine (which, by the way, is not obtainable on prescription, as there is no such preparation on the market, but is presumably intended to mean adrenalin) is advised to be given by the mouth, contradicting statements in the Journal A. M. A. and elsewhere which indicate that this drug is useless given in this manner; and here, be it noted, this remedy, in a dose of only five drops on the tongue, is classed as a "quick acting" cardiac stimulant.

There are a number of other references to the effective administration of adrenalin by mouth, a few of which will be referred to shortly. It should be understood, however, that such fundamental errors as the one under discussion are due to the drawing of conclusions from laboratory experiments alone. We grant that adrenalin is "digested" in the test tube. It is easy to prove that it cannot be recovered from the gastric contents after being in the stomach for only a short time. None will deny that it is rapidly and thoroughly oxidized. But adrenalin is also very easily absorbed, as every rhinologist knows and as any physician can quickly find out if he cares to hold a dram or two in his mouth for a few minutes. Is it not possible, then, as the writer suggests, that the factor of destruc-

tion in the stomach is not concerned at all, but that much or all of the active principle is taken up by the mucous membrane of the mouth, palate, esophagus, and cardia, thus enabling it to exert its therapeutic effects and to maintain its reputation as a "quick acting" remedy when given by mouth?

In connection herewith it should be recalled that the administration of hormones—and adrenalin is certainly a hormone and has been quite properly called the "chromaffin hormone"—brings about physiological effects in two ways: First, by the direct action of that part of the actual substance administered; and, second, by the increased production by the organism of the hormone corresponding to that which is given. In other words, when we give adrenalin, not only do we get the direct drug effect from the dose which is absorbed, but at the same time we are increasing the capacity of the adrenal medulla to produce more of its chromaffin hormone.

We know, from many experiences with thyroid therapy, that with a presumably normal or even a slightly deficient thyroid, certain doses of thyroid extract will bring about symptoms of hyperthyroidism the results of which are not directly due to the drug administered, but to the increased thyroid activity, and these results remain long after the comparatively small amounts of thyroid which were given have been used up. This shows that the principle of homostimulation applies to normal as

well as disordered glands, and this is just as possible with the adrenals as with the thyroid.

To lend emphasis to the position taken by the writer, as well as to Boogher's brief but interesting communication, a few clinical reports from recent literature may be collated here with advantage:

Hutinel (*Arch. de med. des enfants*, February and March, 1915) recommends three or four drops of adrenalin solution one in 1,000, diluted, every two or three hours, as a part of the treatment of severe infectious diseases in children. Each child may receive as much as twenty minims a day by mouth, and Hutinel remarks that he has never obtained so much benefit from the usual supporting measures and that the effects are remarkable even in the gravest cases, since the blood pressure is increased and there is an immediate response in the general mental and physical condition, while the pulse rate is reduced and diuresis is favored.

M. H. Smith (*Medical Record*, October 2, 1915, p. 586) reports having successfully treated several cases of Rocky Mountain spotted fever with ten drop doses of adrenalin solution every four hours. This obviated the prostration common in these cases, convalescence was established earlier than usual, and there was an apparent beneficial effect upon the course of the disease. That the remedy given by mouth was "quick acting" is emphasized by Smith's remark that within a few minutes of the administration of each dose, a fullness of the

pulse and a fading of the eruption were noticeable.

Not much has been done in this country with the use of adrenalin for the treatment of nephritis, though at least five articles have appeared in current Italian medical literature speaking well of this method. The most recent reference is abstracted in the Journal A. M. A., June 10, 1916. This abstract from Il Policlinico (April 30, 1916) may be cited in full: "Borelli reports two cases of acute and one of chronic nephritis in which remarkable benefit was realized by epinephrine\* treatment. One patient was a child of nearly five years, the others were men of fifty and sixty-two. He gave the child sixteen drops a day of a one in 1,000 solution of epinephrine, four drops at four hour interval. The adults were given forty drops a day, eight at a time. Ercolani called attention, in 1910, to the benefit from epinephrine by the mouth in nephritis, commending the harmlessness, ease, and efficacy of this method of treating kidney disease, which has proved its usefulness again and again, and Borelli's experience has confirmed this."

Previous to this report another exhaustive study on the subject was published by Silvestri (Gaz. d. osp. e d. clin., September 1, 1915), in which he analyzes the reports of a number of other clinicians, adds several personal experiences, and proves that

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\*"Epinephrine" is the term used uniformly in all the publications of the American Medical Association, although in this instance the title of Borelli's original article is: "Cura della nefrite con la soluzione di adrenalina nella pratica di condotta."

adrenalin is a most valuable aid in the acute stages of nephritis, but of little value in chronic conditions. He also tells of the experiences of Fede, who found this procedure comparatively more effective in children, since in them the elasticity of the renal glomeruli and tubules is greater, while the adrenal glands are proportionally larger in children than in adults (presumably being more susceptible—quantitatively—to the homostimulant action referred to previously). Silvestri suggests that 1 or 2 minims of the 1:1000 solution of adrenalin chloride be dropped on the tongue every three hours—the total amount given being regulated by the clinical response. For adults the dose may be larger.

There are also numerous reports in the literature of the therapeutic efficacy of total adrenal gland, and of course this is given per os in tablet form. In a recent monograph on "Drug Therapy of Cardio-vascular Diseases," Satterthwaite (Int. Clinics, 1, 1916, p. 26) recommends desiccated adrenal gland as a useful vasomotor tonic in doses of two and a half grains three times a day, and remarks that single doses as a rule will relieve palpitation in a comparatively short time. The active principle of the desiccated gland is naturally similar to that which is available in a pure state, and the favorable experiences with total adrenal gland therapy, by mouth of course, is additional proof that the position of those who have contended that the oral administration of adrenalin is useless, is fallacious.

## XX

### THE ADJUNCT TREATMENT OF TUBERCULOSIS WITH CERTAIN ORGANIC EXTRACTS

AS the years go by our ideas regarding the treatment of tuberculosis are modified, and in no phase of therapeutics do opinions change so much. About 1890 Professor Koch discovered a therapeutic wonder in tuberculin, but its vogue was short-lived, for the intricacies of dosage had not then been learned. Less than ten years ago hyperalimentation was the fashion, and, as with fashions in other things, it was carried to extremes. Nowadays tuberculin has regained its place, but its application is almost an obsession, and the devotion of some practitioners to tuberculin in one form or another seems to show that the fashion has changed again.

There appears to be an idea, almost universal, that as tuberculosis is an invasion of the body by a certain bacillus, the treatment must needs be directed primarily towards the destruction of these organisms and the neutralization of their toxic products. That this is essential none will deny; but, unfortunately, the view is much too narrow. Tuberculosis is first and foremost a condition of lowered resistance in which the infective process has become so prominent as quite to overshadow

the original and by far the most important defect. The following extract from a recent editorial (1) aptly states the matter in the plainest of language:

"The cause of active tuberculosis must now be sought in something which destroys our tolerance, and permits our own lesions to develop. Chief among these causes are the acute infections. . . . In addition to these infections anything else which lowers the general health may thus interfere with that constant production of antibodies upon which our tolerance depends. We can definitely trace many cases to a long period of overwork, alcoholic excesses, exposure to wet, or adverse climate conditions. Indeed, anything which interferes with a perfect condition of health may allow the spread of a focus of infection which we had carried around for a half century or more. Even senility itself may do this. Many men carry the pneumococcus in their mouths all their lives, only to be killed by it in the end; and we must now look upon the tubercle bacillus in the same light of a constant companion, harmless as long as we remain in good condition, but a malignant enemy the instant our guards are lowered."

It is admitted that the good results of the hygienic methods at present in vogue are evidence that a general building up and restoring of the vitality is needed, but, after all, is not this merely a passive form of resistance? Some more active adjunct would be welcome, and it is believed that such will

be found in a consideration of the internal secretions as well as of the possibilities of organotherapy as an auxiliary method of treatment.

Arnold Lorand, in his interesting book "Old Age Deferred," points out that when the usual sanatorium treatment is having its good effects there is a local disintoxication, and the cells of the lungs are co-operating in this process in a manner analogous to the internal secretion by the cells of other glandular structures. This may be one reason for the fleeting advocacy by some of extract of lung-tissue as a remedy in pulmonary disorders. (2, 3) Lorand continues:

"It is a positive fact that under-nutrition (or defective nutrition) through lack of the necessary amount of proteids in the diet exposes one more to infection by the bacilli. . . . The findings of Gratzlitz indicate that an insufficient proteid diet predisposes also to anemia. The importance of this fact is emphasized by Sajous, who has shown (1903) that defective nutrition weakens the activity of the pituitary, thyroid and adrenals, the secretions of which take an active part in the destruction of bacteria and their toxins." (4)

The usual general manifestations almost invariably present in cases of tuberculosis—fever, lassitude, and diminished metabolism—can not but be accompanied by disturbances of a similar nature in the work of the internal secretory organs. Perhaps the importance of these functions, many of

which are as yet little understood, is even greater than we think, and certain facts can bear much emphasis and repetition. Professor Schafer, in his presidential address before the British Association, June, 1912, (5) says: "The second essential condition for the maintenance of the life of the cell-aggregate is the co-ordination of its parts and the due regulation of their activity, so that they may work together for the benefit of the whole. . . . The activities of the cells constituting our bodies are controlled in another way than through the nervous system—viz., by chemical agents circulating in the blood. . . . These substances have received the general designation of 'hormones,' a term introduced by Professor Starling. Their action, and indeed their very existence, has only been recognized of late years, although the part which they play in the physiology of animals appears to be only second in importance to that of the nervous system itself; indeed, maintenance of life may become impossible in the absence of certain of these hormones."

When we consider all the emphasis that has been laid upon the importance of the internal secretions, it seems strange that their relation to tuberculosis is rarely mentioned. Treatment based upon the regeneration or regulation of these important glandular functions is quite the exception, and will continue to be until the importance of their relation to the original cause of tuberculosis is realized.

Our French colleagues, always more alert in the application of measures "on the border-line of progress in therapeutics," have for some years been emphasizing the importance of "Les Opotherapies dans la Tuberculose," and a valuable resume with the above title was recently published. (6) In this article reference is made to no less than fourteen distinct forms of opotherapy, of which perhaps only one—the use of red bone-marrow—has found any favor in England and America.

It would seem that the most important phase of the organotherapy of tuberculosis is unquestionably the use of spleno-pancreatic extracts. Next in importance is the use of preparations from the liver, and the value of these methods is enhanced by the administration of secretin—a hormone prepared from the pylorus and duodenum.

With the use of extracts of thyroid, pituitary, adrenal, lung, ovary, and testes, I have had no experience, and although numerous references to these various subjects can be found in the medical literature, especially that of France and Italy, the remainder of this article will be devoted to brief consideration of the forms of organotherapy first mentioned—the use of the extracts of spleen, pancreas, liver, and duodenum.

Practically every form of organotherapy that is recommended in tuberculosis is useful only as it influences nutrition, and this is essentially true of the use of splenic extract. In an exhaustive paper

on the subject, (7) the writer has gathered together some information regarding the fundamental functions of the splenic hormone, and concludes that the value of splenic extract in practical therapeutics may depend on the occurrence of a hormone or hormones which are concerned in the defenses of the blood in tryptic and intestinal digestion in the reparative processes, and in certain specific functions on the part of the spleen itself. Bayle, of Cannes, has obtained results which he regards as almost of a specific nature, and in his paper, read before the last International Congress at Rome, (8) he concludes:

“I feel authorized by my results to call splenic opotherapy a specific treatment for tuberculosis. It is a specific from the therapeutic viewpoint, because it modifies the soil, rendering it less suitable as a medium for the culture of the bacillus of Koch. It is a specific from the practical viewpoint because it manifests all the function and rapidity of action of a specific medication. Employed in convalescents it prevents tuberculosis by increasing the mineral content of the tissue (*en remineralisant le terrain*). Employed in confirmed cases of tuberculosis it cures them.” Bayle has recently given a very concise resume and bibliography of his entire work on this subject. (9)

Schroder, (10, 11) Superintendent of the Neuen Heilanstalt fur Lungenkrankheit, Schomberg, along with his colleagues there, has made an ex-

tensive series of experiments on puppies and guinea-pigs, and concludes that the administration of spleen extract exercises a powerful influence against the progress of inoculation tuberculosis in these animals. "The minimizing effect of the spleen extract was obvious, insuring a longer duration of life and milder lesions in the animals treated, as compared with the control animals."

Van Stockum, (12) of Amsterdam, has carried out a series of interesting tests in the treatment of tuberculosis with extract of spleen previously exposed to the X-rays. His report on 3,000 cases so treated is convincing evidence that the use of this preparation is followed, especially in the surgical forms, by an early betterment. He also lays stress on the harmlessness of this method. In a recent editorial (13) appears a statement which deserves emphasis: "The subject is certainly one that should not be lost sight of, and practitioners may well remember that advantage may accrue from the use of splenic substance as an adjuvant at any rate."

Tuberculous patients are invariably sufferers from toxemia, not only the specific toxemia, but also that due to stagnant digestive functions and deficient detoxicating power. We know that the successful use of various liver extracts for a number of years definitely has proved that they have a noticeable detoxicating power, (14) due doubtless to the fact that the internal secretion of the liver has this property. This is probably the cause of

much of the good that has resulted from the use of this class of preparations. Lemoine and Gerard (15) have brought forward a petroleum extract of bile called "paratoxine," which is said to be useful in tuberculosis, chiefly on account of its antitoxic action.

In studying this subject, and applying it in their extensive clinical work in Paris, Gilbert and Carnot (16, 17) found that liver extract possessed an antihemorrhagic influence, and they used it in the treatment of hemoptysis, especially in tuberculosis, with very encouraging results. In cases where tuberculosis is associated with hepatic enlargement and derangement this form of organotherapy confers great benefit. H. Parmentier (18) reports that liver extracts have a generally good influence in tuberculosis, causing an increase in weight as well as a decrease in the night sweats and number of bacilli in the sputum. His experiences confirm those of Gilbert and Carnot, which proved the value of liver preparations in hemoptysis.

It has been frequently suggested that the therapeutic value of codliver oil is due in considerable part, not to the contained fat, but to a certain internal secretion of the liver of the cod. This may act directly, or, more likely, according to Leonard Williams, (19) by stimulating one of the normal internal secretory glands, the secretion of the one so stimulated being inimical to the development of the tubercle bacillus. It is a significant fact, he

adds, that the darker and more crude the codliver oil the more efficacious it is.

The pancreas undoubtedly plays an important part in defending the body against infection. In proof of this one has only to remember the frequency with which diabetics suffer from boils and local infective processes, and the remarkably high percentage of diabetics that suffer and die from concomitant tuberculosis. This leads one to believe that the pancreas, in addition to its known functions, plays an important part in regulating resistance to infection. Brieger (20) has shown that pancreatin lowers the abnormally high antitryptic index of the blood in tuberculosis, and predicts that eventually treatment will be on the lines of a combination of pancreatin and tuberculin. Strubell (21) has made the definite statement that pancreatin administered per os increases the opsonic index to the staphylococcus. This may explain some of the encouraging results obtained from spleno-pancreatic-opotherapy in tuberculosis, and also the benefit to the diabetic which often follows pancreatic therapy. Referring to this, the editor of the Medical Record (22) says: "The future may witness the routine use of pancreatin in tuberculosis . . . and in many chronic affections with lowered opsonic index."

Digestion is almost invariably poor in tuberculosis, and, unfortunately, in no class of disease is a vigorous digestion more necessary. The tendency

to push the feeding of the consumptive often over-taxes digestion, and where hyperalimentation is necessary, or where decreased digestive capacity has already made itself manifest, secretin is a most reasonable and useful remedy.

As originally shown by Bayliss and Starling, secretin is a specific chemical activator of pancreatic function, produced in the duodenal walls. Secretin actually combines with the precursors of the pancreatic digestants and is used up in their formation. Other investigators have shown that this influence is not confined to the pancreas, but that secretin stimulates both the peptic and the oxytic glands of the stomach, as well as those glands which produce the succus entericus, and some French investigators pointed out that secretin also stimulates the liver. Whether the influence of secretin is or is not as widespread as has been stated above, there can be no doubt that it has a salutary influence upon digestion, an influence nowhere more essential than in the treatment of tuberculosis. Boardman Reed draws attention to the organic derivatives as valuable factors in the treatment of indigestion, and gives his experiences (23) with a preparation called "secretogen," which contains gastric and pancreatic secretins and enterokinase, with 0.5 per cent. HCl. It has proved in a number of cases to be much more effective than the usual pepsin-HCl combinations, rapidly bringing the stomach up to normal, and improving the

intestinal digestion and assimilation. The author gives the result of gastric analysis made in one of the cases, in which secretogen was suspended for a month. The proportions of both free and combined HCl were found to be still a little above normal, though before the remedy was taken there had been no free HCl at all, and the proportions of both combined HCl and total acidity were below normal.

The importance of hormones in the treatment of disease is daily being more fully recognized, and there is little doubt that before long their value as an adjunct in the treatment of tuberculosis will be generally accepted. The results already published admit of no doubt, and are sufficient at least to disarm skepticism. We have not found a panacea for tuberculosis, nor are we likely to find one soon; but it can not be gainsaid that the control of the body functions as a whole—and especially that control aimed at in an attempt to regulate the hormone balance—will be eventually a very important factor in the successful treatment of tuberculosis. We shall do well to bear this in mind, not forgetting that “an attitude of obstinate unreceptive skepticism leads only to stagnation and death, and has certainly no place in an atmosphere where men are striving to unravel difficult and elusive problems.” (24)

The successful therapist owes his position to a thorough attention to detail, no less than to his appreciation of probabilities, both diagnostic and

therapeutic; and if the possibilities of hormone therapy materialize, as they bid fair to do, there is every hope that the prevention and cure of the great white plague eventually may become an accomplished fact.

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Some years have elapsed since the foregoing pages were written. On reading them over I am reminded of some comment which I heard in London some months after this paper first appeared in print: Organotherapy is no more efficacious in the cure of tuberculosis than any other of the hundred and one therapeutic offerings.

Of course this has more truth in it than fiction and it may be well to state unequivocally that none of the measures outlined are "cures"—the chapter heading calls them "adjuncts."

However, of one thing I am convinced and that is that pancreatin is indeed a valuable remedy in tuberculosis, and that it acts in two separate and distinct ways. Besides its beneficent effects upon digestion, pancreatin seems to antagonize excessive adrenal activity, and it is now believed by several prominent investigators that the toxemia of tuberculosis irritates the adrenals quite considerably and this hyperadrenia is responsible for several of the sympathetic symptoms such as dryness of the mouth, irritable heart, digestive crises and some of the sympathetic nervous derangement not uncommon in the tuberculous.

Whether or no we use organotherapy in treating tuberculosis, we must at least realize more than we have done that the tuberculous patient has an endocrine system which is very likely to be affected early in the course of the disease, and that if this is true, and how can it but be, the endocrine phase of tuberculosis is worth studying in the light of our present knowledge of the importance and all-embracing effects of the endocrine principles in health and disease.

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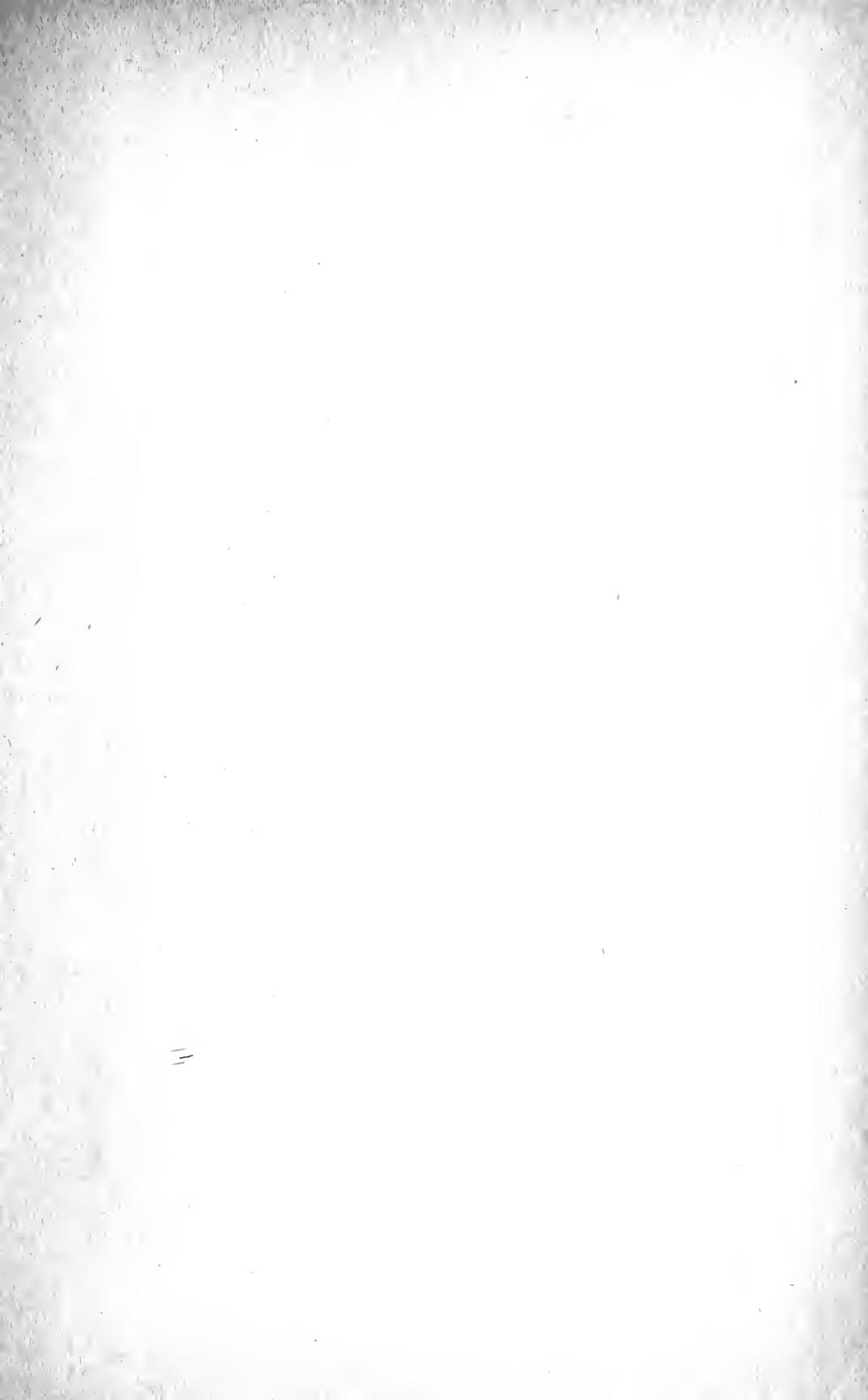
Original communications, each accompanied by the comment of several, thus broadening their value to the reader.

A review department containing numerous abstracts of current literature on the internal secretions, conveniently divided into four sections—General, Experimental, Clinical and Therapeutic.

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ENDOCRINOLOGY is an up-to-date resume of the subject and is but a part of the advantages of membership in this Association. The Secretary, Dr. Emil Goetsch, Johns Hopkins Hospital, Baltimore, Maryland, will be pleased to send further information to interested physicians on request.

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